Differential Diagnosis of Internal Diseases

A.V. Vinogradov

Volume 1

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А. В. Виноградов

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Differential Diagnosis of Internal Diseases

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Foreword

The achievements of science and technology in recent years have made the recognition of internal diseases notably easier and broadened our understanding of many problems of their clinical characteristics and pathology. Despite the great number of auxiliary methods of examination, the physician often, as before, comes up against considerable difficulties in solving general diagnostic problems. This is to a certain degree the result of the continually growing specialization of physicians as well as of some shortcomings in the methods of training at medical higher schools.

More and more physicians are specializing in the study of some one functional system of the body. Although specialization is among the progressive developments, it has its demerits. The physician specializing in diseases of some organ is often nonplussed when confronted with a problem in differential diagnosis when the results of the examination of many systems of the body must be generalized. He can be helped by a consultation, but such consultations are usually held in really difficult cases, whereas questions of differential diagnosis often have to be decided in practice by the doctor at the bedside of practically every newly admitted patient.

The manuals dealing with various methods of examination such as electrocardiography, phonocardiography, echocardiography, clinical biochemistry and roentgenology written by narrow-field specialists are of undoubted value but in relation to the art of diagnosis they are like pieces of smalto in mosaic work: although different in size, shape and colour they can become a beautiful Ravenna mosaic only in the skilled hands of an experienced craftsman. In exactly the same way the results of different methods of examination may explain the cause of the disease only to an experienced clinician, while they are often useless to physicians who are not skilled in the art of differential diagnosis.

The system of training adopted at Soviet higher medical schools is based on the gradual ascent from the general to the particular, from the disease to the patient. The future doctor gradually accumulates knowledge in the pathological anatomy, pathogenesis and the clinical aspects of various diseases, e.g. tuberculosis, rheumatism, lymphogranulomatosis, and iron, vitamin B_{12} or folic acid deficiency in the body. The main advantage of this strictly consecutive method consists in the fact it provides an insight in the funda-

mentals of knowledge according to speciality in a comparatively short span of time.

On graduation the physician soon realizes that his daily practice runs in a direction that is directly opposite to the abovedescribed, to be more precise, the patient comes to him not with defined diseases, but with complaints. Even the most scrupulous clinical examination fails to provide a picture of tuberculosis, lymphogranulomatosis or of any other disease. Chances are that the best that can be achieved is the detection of one or more syndromes which are equally or nearly equally often encountered in several diseases.

Many excellent monographs on different diseases have been published, but they discuss the diagnosis of a known disease and the features distinguishing it from other, also already known diseases. The ultimate result of the usually very difficult and protracted diagnostic work of the physician in such cases is taken as the initial point of analysis. In the first Soviet manual concerned with the differential diagnosis of internal diseases that is offered to the reader the abovestated paradoxical situation has been successfully overcome.

The system of concepts proposed by A. V. Vinogradov is praiseworthy for its complete accord with the daily diagnostic work of the physician at the patient's bedside. It begins by analysing the results of the clinical methods of examination and ends by clarifying the aetiology of the disease. Many years of experience in medical and pedagogical work enabled the author to describe the system of differential diagnosis practiced in his clinic in a way that is both brief and clear. This, of course, is not the only possible system, but it may provide guidelines for other internists to work out their own systems for analysing complicated clinical syndromes.

The manual is not only based on the author's extensive personal experience but on the detailed study of literature on the subject published in the USSR and abroad. The author focuses particular attention at interpreting the results of special diagnostic studies suggested in the last decade. The explanatory style of narration makes it easier to absorb the vast amount of factual material that has been collected on the subject of internal and associated diseases.

It is hoped that the recommended manual on the differential diagnosis of internal diseases will serve as a handbook at the disposal of internists helping them to master the art of differential diagnosis.

Academician E. I. Chazov.

Introduction (The Method of Differential Diagnosis)

The principal difficulty in making a diagnosis consists in the fact that many internal diseases have no constant symptoms or signs. The same disease, such as tuberculosis, for instance, may be manifested first by one symptom, and then by another. If we should add that the same symptoms and signs are encountered in many different diseases it becomes apparent that the physician must be specially trained to perceive the causes of many different clinical syndromes.

The ever increasing number of instrumental, biochemical and biophysical methods of examination oblige the modern physician to devote much time to studying and interpreting the results of a multitude of tests. It would be difficult to overestimate these tests in solving particular problems of the diagnosis of internal diseases, but it should also be borne in mind that their volume and character are determined primarily by the results of ordinary clinical methods of examination which we have accepted as the starting point of the diagnostic process.

The monographs devoted to different diseases provide detailed descriptions of the methods of their diagnosis, followed usually by brief information about the features distinguishing the given already known disease from other diseases which are also known, e.g. what distinguishes ulcerative colitis from Crohn's disease. The terminal point of the diagnostic work of the physician in such cases is taken as the initial point of the analysis. This paradoxical state of affairs can be explained by the insufficient attention paid by the authors of monographs to the art of distinguishing one disease from another, accepting the complaints of the patient and the results of his examination as the starting point of analysis. This manual has been written with the aim of making up the deficiency in this direction of diagnostic thinking.

The experience of many years of medical practice permits us to assert that the art of differential diagnosis can only be mastered at the patient's bedside, because it is only right next to the patient that the doctor can most rapidly perceive one of the basic premises of differential diagnosis, namely, that the detection of pathological symptoms and signs is obligatory, but not always sufficient for making a correct diagnosis. This is explained both by the changing value of one and the same sign in the course of the disease, and by

the frequent need to base one's diagnostic conclusion on the shades of the symptoms and signs of the unknown diseases.

Moreover, a situation fairly often shapes at the patient's bedside in which not only the symptoms but even the signs of a disease are of less diagnostic value than the clinical picture against the background of which they are manifested. To illustrate the point let us refer to the appraisal of the third heart sound which, depending on the clinical context, may be either the manifestation of the active diastole of a healthy heart or 'the cry for help of an ailing heart'.

The ability of correctly assessing the clinical background against which the signs of the disease are manifested is either achieved by the trial and error method or learned from a teacher. Although this ability cannot be attained by reading books, we think a manual on differential diagnosis is nonetheless necessary because it provides the doctor with the complex of basic knowledge required for tackling the given problem and outlines the main lines for analysing the facts which he brought to light in examining the patient.

Among the methodical means commonly used is the skill and habit of making a quantitative assessment of each detected sign. The physician is given invaluable assistance in this direction by the results of modern instrumental and biochemical methods of investigation. These methods are so complex and numerous that the internist usually simply limits himself to the knowledge of their diagnostic possibilities, learning to appraise the results of these tests in the light of the peculiarities in the clinical picture of the disease. It is most important to learn to sense the need and expediency of applying special diagnostic methods to the patient being examined. This intuition is born of the accumulated experience in diagnostic work, of the ability which gradually develops in the process of this work to appraise not only the symptoms and signs of the disease, but the patient himself as a personality.

The general appraisal of the patient is greatly helped by a detailed conversation not only about his complaints, but about his occupation, the particular ways of spending his free time, of his habits and attachments. It would be hard to overestimate the diagnostic value of a heart-to-heart talk with him. Unfortunately, the ability of putting the patient at ease is not shared by one and all, because the mastering of this art not only requires a responsive heart on the part of the doctor, but a sound reserve of professional knowledge and general culture which cannot be acquired off-handedly, but is stored up in the duration of one's whole life.

The diagnostic work begins during the talk with the patient and his immediate examination. During this talk the doctor usually forms some sort of diagnostic hypothesis in the light of which there is often an involuntary 'adaptive' interpretation of the detected symptoms and signs.

A consequence of this, unfortunately widespread error in thinking, is the loss of objectivity in summing up and appraising the results of the examination. This error is unlikely to be made only by that doctor who is willing to reject any, even the most 'brilliant', hypothesis as soon as it is evident that it contradicts the facts gradually accumulating during examination of the patient.

Particularly close attention should be paid to the collection of facts. Even experienced physicians feel that it is necessary to examine the patient again and again so as to gain a more precise picture of the development of certain signs of the disease, paying special attention to the search for new signs arising during the period of observation and to the character of changes in the degree of manifestation of old signs. Persistently repeating vomiting, for example, predominates in the clinical picture of many diseases. It may be the foremost sign of ileus of the small intestine, the 'periodic syndrome', many cases of acute gastroenteritis, crisis in Addison's disease, or of a precomatose state in diabetes mellitus. However severe this vomiting may be, and whatever its duration, its diagnostic significance must always be reconsidered time and again, depending on the evolution of the attending signs in repeated examinations of the patient: the colour and odour of the vomited material, abdominal distension, the rate of alkalosis or acidosis development, etc.

Signs which contradict the shaping diagnostic hypothesis and have no satisfactory explanation from the standpoint of the presumed diagnosis should be scrupulously watched and rechecked continuously. It is known that the complete absence of stercobilin in the faeces is a reliable sign of cancer with compression of the biliary tract. Do not rule out the presumed diagnosis of acute virus hepatitis in your patient if complete obstruction of the biliary tract is revealed. The diagnostic significance of acholia of the faeces revealed in repeated tests should be reappraised, depending on whether the absence of stercobilin is temporary, intermittent or permanent.

The process of differential diagnosis begins with the critical evaluation of the symptoms and signs of the disease detected in examination of the patient. This is the most crucial stage in the analytical work of the physician. The disclosed signs are grouped according to the degree of their apparent importance and their presumed interrelationships. The diagnostic work is greatly simplified if the detected signs can be combined into one or two syndromes. It becomes quite easy if one of the signs proves to be pathognomonic of some disease. For example, *Plasmodium malariae* is found in a thick drop of blood of a feverish patient. Unfortunately, such cases are very rare in the practice of the clinic for internal diseases. In most cases the signs and symptoms detected during the examination of

the patient prove to be characteristic not just of one, but of many diseases.

The next stage of diagnostic analysis consists in distinguishing the syndrome or syndromes which are predominant throughout the course of the disease or just during one of its periods. One has to know the main signs and regular patterns in the course of many diseases to be able to distinguish the dominating syndrome. This knowledge is acquired at the patient's bedside in discussing the course of the disease with teachers and colleagues and in reading special literature on the subject.

Triple cardiac rhythm, for instance, in combination with a systolic murmur, oedema, and enlargement of the liver and spleen may be encountered both in heart failure and in constrictive pericarditis; splenomegaly in the first of these syndromes, however, appears only in the late stages of the disease, whereas in the second syndrome it is already found at the early stages.

In solving the problem of the relation of the detected sign to this or that syndrome, it is essential to take into account not only the time of its appearance, but the degree to which it is manifested and its reversibility under the effect of therapeutic measures. Venous pressure is usually lower in heart failure than in constrictive pericarditis. In some cases of heart failure, however, venous pressure may be just as high as in constrictive pericarditis, but in heart failure it may noticeably diminish under the effect of therapy and even reach normal level, whereas in constrictive pericarditis it remains at a high level irrespective of the manifestation of other signs of the syndrome.

The physicians of past generations thought it necessary and useful to explain all the symptoms and signs detected in the patient who was assumed to be sick with one disease. At present this rule cannot be accepted unconditionally. In view of the change in age of the main contingent of patients in internal disease departments, and also in connection with the introduction of more effective methods for treating many diseases that were formerly regarded incurable, in our time a patient sometimes proves to have not just one, but two and even more diseases at the same time. It is particularly important to bear this in mind when examination of a patient discloses two simultaneous clinical syndromes which seem to be in no way connected: e.g. purpura and proteinuria, acute abdominal pain, ataxia and the absence of tendon reflexes.

In such cases each of the detected syndromes must be reason enough for an independent diagnostic analysis. If the patient suffers just from one disease, the separate diagnostic analysis both of purpura and proteinuria will lead up to an identical diagnosis, e.g. multiple myeloma. If the patient is suffering from two diseases, the diagnostic analysis of abdominal pain and of the cause of the affection

of the central nervous system may result in establishing the diagnosis of two independent diseases, e.g. tabes dorsalis and acute appendicitis.

In his everyday practice the physician usually encounters the most widespread diseases. Pain in the region of the heart most often proves to be the consequence of angina pectoris or myocardial infarction, and pain in the abdomen of acute appendicitis. Abdominal pain in the patient, however, may be caused by myocardial infarction, and pain in the region of the heart by pancreatitis or osteochondrosis of the cervical spine. It is important to clarify which disease caused the symptoms and signs found in the patient, while it is not at all important whether this is a rare or frequent disease.

The conviction that diagnostic analysis must be performed impartially may be derived from a book, but the ability to conduct this analysis impartially is developed only at the patient's bedside, and, at first, under the supervision of an older and more experienced colleague.

The diagnostic analysis ends with the making of a provisional diagnosis which may be considered final only if in the light of this diagnosis it becomes possible to explain the cause of all the symptoms and signs found in the patient during examination. In considering the diagnosis at this stage special attention should be paid to the negative signs: for instance, one should not fail to supply a satisfactory reason for the absence of a diastolic murmur in a patient whose disease has been diagnosed as mitral stenosis, or to explain the cause of the negative results of blood cultures of a patient in whom the diagnosis of bacterial endocarditis is made.

The final diagnosis is formulated only after a discussion and conclusion on all positive and negative symptoms and signs revealed in the patient in the process of examination.

The wish to make maximum use of the given volume of this book for purposes of differential diagnosis made us present the material in a very concise manner, at times in the form of a synopsis. It was also decided to delete such illustrative material from the context as excerpts from case records, the results of X-ray, phonocardiographic, scintigraphic and other types of examination. Although such material is very valuable, it nonetheless is not absolutely necessary for the purposes of differential diagnosis. Besides, if it were included, this manual on differential diagnosis would have become an ordinary book interpreting the results of certain methods of examination.

The book is intended for a qualified internist; this is why data on the pathogenesis of the syndromes that are discussed have been reduced to a minimum or simply deleted. They should be known to the reader.

Chapter I

Abdominal Pain

Three types of pain in the abdomen are customarily distinguished, namely, visceral, somatic, and referred. Each of the types has its own characteristic features the knowledge of which makes it easier to establish the cause of the painful sensations.

Visceral pain arises directly in the affected organ. It is of distressing character and is usually attended with sweating, nausea, vomiting, and the patient turns very pale. All attempts made by the patient to relieve the pain by changing, for instance, the position of his body in the bed fail. Depending on the affected organ, this pain may be located, though with difficulty, in the epigastrium, the umbilical region or above the pubic symphysis.

Somatic pain is induced by stimulation of the parietal peritoneum. It is distinguished by great intensity and the patient points to the place where he feels it. In acute appendicitis, for instance, pain may be exactly located in McBurney's point. Cough and movements intensify somatic pain sharply.

Referred pain was studied for the first time by Zakharyin and Head. It arises from very intensive stimulation of the affected organ and is transmitted over the entire neurosegment and is sometimes even referred to the adjoining segments. Referred pain in the abdomen is encountered in diseases of the brain, meninges and many other internal organs. The ability to distinguish referred pain from somatic pain underlies the differential diagnosis between acute abdomen, which calls for emergency laparotomy, and abdominal pain in which surgery is contraindicated.

The wide range of pain sensations from quite endurable discomfort to unbearable suffering, which we judge from the patient's complaints and behaviour, may yield valuable diagnostic information on purposeful interrogation. All patients must therefore be questioned in detail about the pain in the abdomen. It is first of all necessary to establish how long ago the pain sensations had appeared. Chronic pain, even if intensive, gives the physician enough time for the diagnostic examination.

Particular attention should be paid to pain that had appeared only recently because it may often herald acute abdomen. The pain intensity itself is of no decisive diagnostic significance and indicates neither its hazardousness for the patient's life nor the need

for surgical intervention. Continuous pain arising from irritation of the peritoneum is particularly dangerous. Intermittent attacks of pain (colic) are typical of diseases of the hollow organs.

It is also necessary to locate the pain, and establish whether it is referred or whether it migrates. Pain arising in the shoulder simultaneously with abdominal pain is evidence that the diaphragm is involved in the morbid process. Pain in appendicitis often appears first in the pit of the stomach or around the umbilicus and moves to the right iliac region only later. Symptoms and signs attendant to the pain are of diagnostic significance; these are nausea, vomiting, diarrhoea, jaundice, anuria, haematuria, and a decrease or increase in the pulse rate. It is general knowledge that the periodic occurrence of pain and its association with meals or medication with some drugs help greatly in making the diagnosis.

The intensity of the abdominal pain and the extent to which its cause endangers the patient's health and life vary irrespective of each other.

Mild pain in walled off perforation of a duodenal ulcer is an indication for emergency surgery which is contraindicated even in excruciating pain arising, for instance, in tabetic crisis or diabetic keto-acidosis. On account of the limited practical significance of this sign, it is expedient in some cases to distinguish diffuse and localized abdominal pain. Diffuse pain is felt in the whole abdomen, localized pain only in one of its regions.

Diffuse peritonitis is a classical example of diffuse abdominal pain. On appearance such pain is always attended with signs of peritoneal irritation, i.e. tonic rigidity of the abdominal muscles and positive Shchetkin-Blumberg's sign. Diffuse abdominal pain may also occur as colics. In such cases it is caused by periodical strong contractions of the smooth muscles of the hollow organs in the abdomen and retroperitoneal space and not by irritation of the parietal peritoneum. Localized pain, particularly if attended with signs of peritoneal irritation, may prove a forerunner of diffuse peritonitis when the surgeon undertakes unreasonable tactics.

From the very first days of practice in a town hospital the internist becomes convinced that he must possess subtle knowledge of the differences between referred abdominal pain and pain arising in localized and diffuse peritonitis (Supplement I-1*). The results presented below of the discussion of these differences in the light of our many years' experience may help the physician to some extent in becoming proficient in differentiating these types of pain.

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*The supplements are given at the end of the chapters.

Diseases of the Lungs and Pleura

It has been known since long ago that **pneumonia and pleurisy** may be accompanied by the acute abdomen syndrome. A cavitary operation endangering the patient's life in such cases may be avoided if the manifestations of the pain syndrome are compared with the simultaneously occurring objective signs of the disease. We think that the following features of the pain syndrome prove valuable in discussing the differential diagnosis between pneumonia and true (surgical) acute abdomen.

Acute abdominal pain with signs of peritoneal irritation is encountered only at the onset of pneumonia, which may be bacterial, viral, lobar or microfocal. It is our experience that signs of peritoneal irritation attend acute respiratory diseases only when these are complicated by pneumonia. It stands to reason that pneumonia does not necessarily develop in the first days of an acute respiratory infection. A patient with diffuse peritonitis, even if he is in a grave condition, always recalls the moment when the acute abdominal pain had appeared. It occurs suddenly and spreads immediately over the whole abdomen. A patient with pneumonia may say that he had experienced severe pain in the abdomen in the morning, after a meal or at night, but he cannot remember the moment separating the period of health from the beginning of the severe disease.

Abdominal pain sometimes precedes the physical and radiographic symptoms of pneumonia. It is always felt in one and the same region, only on the right, as a rule, or less frequently only on the left side of the abdomen. Rigidity of the abdominal muscles is correspondingly found only on one side. In inflammatory diseases of the abdominal organs the defence reaction of the muscles is usually clearly localized. It is always more pronounced over the involved organ (e.g. the vermiform process) than in regions remote from it. It should be pointed out that marked rigidity of the muscles of the whole abdomen is sometimes encountered at the onset of appendicitis in young boys and children, but it is short-lived, lasting one to three hours, after which this 'extended' response is replaced by the usual picture of local tenderness and rigidity of the right iliac region. In true peritonitis the rigid zone never reduces in size.

Progressive localized peritonitis usually spreads either to the upper (above the line of the attachment of the greater omentum to the transverse colon) or lower half of the abdomen. From the upper abdomen the inflammatory process extends behind the ascending colon to the right iliac region; from the lower abdomen (e.g. true pelvis) inflammation spreads along the sigmoid mesentery to the left iliac region. As a consequence of this, rigidity of muscles

in the right iliac region may be caused not only by appendicitis, but by inflammatory processes in the upper abdomen (cholecystitis, perforation of the transverse colon, perforation of duodenal ulcer), whereas rigidity in the left iliac region may be due to inflammatory process in the true pelvis or appendicitis when the apex of the vermiform process is localized close to the sigmoid colon. In diffuse peritonitis the whole anterior abdominal wall is rigid.

Muscular defence in peritonitis is distinguished by constancy. Reflex muscular defence changes in intensity with time. When the attention of a patient with referred abdominal pain is diverted, the rigidity of the abdominal wall may sometimes be overcome and the palpating hand may be pressed deeply into the abdominal cavity. Rigidity of the abdominal wall is constant in peritonitis but inconstant in pneumonia. In repeated examination of the patient it is found to be now intensified, now weakened. Podonenko-Bogdanova (1968) contends that this is associated with the dynamics of the inflammatory process in the lungs. In other words, the pain in the abdomen and the muscular defence in peritonitis remain for several hours without changing and are never encountered separately, whereas in pneumonia one may occur without the other.

It is much easier to make differential diagnosis by analysing the other signs of the diseases that are compared. Pneumonia sets in with fever often attended with a chill that may recur. In perforated gastric ulcer body temperature is at first normal, in appendicitis it is sometimes moderately elevated. Herpetic eruption on the face and hyperaemia of the face are often observed in pneumonia but not in peritonitis. Tachycardia cannot be accepted as a reliable differential diagnostic sign. It is usually attendant to bacterial pneumonia but in some cases with virus pneumonia the pulse rate is relatively decreased. Peritonitis is characterized by increase of tachycardia during the disease. We could never use dyspnoea as a reliable criterion in differentiating pneumonia from appendicitis although other authors claim it to be a valuable differential diagnostic sign. The disparity in opinions is most likely explained by the different age of the patients.

Pneumonia, like fevers of other aetiology, is usually attended with constipation. The onset of peritonitis is often marked by vomiting and diarrhoea, the latter is later replaced by constipation. In peritonitis the board-like abdominal wall does not take part in the act of respiration while the abdominal reflexes are not produced. In perforation of the hollow organs gas escapes into abdominal cavity and its accumulation under the diaphragm leads to the disappearance of the hepatic dullness. The accumulation of free gas in the abdomen is demonstrated by X-ray or by percussion. The results of abdominal auscultation are undoubtedly more valuable in making the differential diagnosis. The peristaltic sounds in the abdomen

are heard every four or five seconds in a healthy individual but disappear or are drastically diminished in peritonitis. In referred pain they do not change.

A patient with peritonitis tries to lie still in bed because each contraction of the abdominal muscles is attended with pain. The knees are often drawn to the abdomen. The tongue is dry and coated. In five to six hours after the onset of the disease the abdomen is gradually distended and at the same time the face takes a characteristic expression (hippocratic face). Vomiting often occurs at the beginning of peritonitis, disappears later, and reappears when localized peritonitis develops into the diffuse form. A patient with pneumonia and referred abdominal pain moves easily in bed and the rigidity (spasm) of the abdominal wall subsides gradually. Rectal examination is characteristically painful in peritonitis but painless in pneumonia.

The localized and diffuse forms of peritonitis are usually marked by leucocytosis of $10 \cdot 10^3$ to $15 \cdot 10^3$ per 1μl and increased erythrocyte sedimentation rate. In pneumonia leucocytosis may in some cases reach $20 \cdot 10^3$ to $40 \cdot 10^3$ per μl, in others the leucocyte count may be normal. Physical and radiographic methods of examination of the chest often disclose characteristic signs of pneumonia, which are not found in peritonitis.

Pneumonia with referred pain in the abdomen is differentiated rather easily from diffuse peritonitis but with great difficulty from appendicitis, particularly in elderly and old patients with retrocaecal localization of the process. In such cases of appendicitis the peritoneal phenomena are mildly pronounced or may even be completely absent. Rectal examination may prove to no purpose because the process is localized retroperitoneally, far from the true pelvis. The final diagnosis in such cases is made from the results of repeated examination of the patient.

Diseases of the Heart

Abdominal Signs and Symptoms in Myocardial Infarction

In some cases with myocardial infarction, pain in the abdomen may be very intense and be the principal symptom. At the beginning of the attack the patient is restless. In an attempt to relieve the pain he often changes his posture in bed. A feeling of extreme weakness and exhaustion develops in attendance to the pain. Abdominal pain and disorders of gastro-intestinal function are relatively rare

in myocardial infarction, but if they do appear they are of very grave prognostic significance in most cases.

Our clinical experience of many years does not allow us to agree with those authors who claim that this is referred pain. Besides the rebound tenderness, pain that is more severe and of a longer duration may be encountered in myocardial infarction; it is caused by acute enlargement of the liver, impaired function of the pancreas, intestinal ischaemia, acute erosions and ulcers of the gastro-intestinal tract, and sometimes also by embolism of the mesenteric arteries.

Destructive changes in the gastro-intestinal tract occur usually in the first days of the infarction. Much less frequently they develop later. Solitary or multiple erosions and ulcers are mostly found in the stomach, but sometimes they are disclosed in the lower part of the oesophagus, the jejunum, ileum, and even in the colon. They are also encountered in the terminal stage of chronic heart failure, in burns, and in some other diseases. Their development is linked with impaired trophic function of the central nervous system and disturbed homeostatic regulation of circulation (Vinogradov et al., 1971). Involvement of all abdominal organs in the pathological process explains the diversity of the clinical syndromes which develop and often have to be differentiated from calculous cholecystitis, perforation, acute pancreatitis, ileus, and other cases of acute abdomen.

Hepatic colic and acute cholecystitis. Myocardial infarction with sharp abdominal pain has to be mostly differentiated from acute cholecystitis or an attack of hepatic colic. Differential diagnosis with calculous cholecystitis attended with attacks of hepatic colic is especially difficult. A scrupulously taken medical history helps in making the diagnosis of the principal disease in many such cases.

Pain in hepatic colic reaches its peak within a few minutes, whereas pain in myocardial infarction intensifies in most cases in a wave-like manner and becomes most severe in approximately 30 or 60 minutes after its appearance. Hepatic colic is attended almost in all cases with nausea caused by increased pressure in the biliary tract. Nausea may also occur in the acute period of myocardial infarction, particularly after morphine administration. The absence of nausea at the peak of the pain attack is indirect evidence in favour of myocardial infarction.

The results of palpation of the right hypochondrium are also of some diagnostic importance. At the onset of the pain, there may be no tenderness in the region of the gall bladder in both diseases. A few hours later the gall bladder in a patient with hepatic colic becomes tender to palpation. The pain intensifies on deep inspiration. Signs of peritoneal irritation often appear. In cholelithiasis

and acute cholecystitis tenderness of the liver, if elicited, is usually restricted to the region of the gall bladder, whereas in myocardial infarction both the right and the left hepatic lobes are tender to palpation because of acute swelling.

Myocardial infarction is often attended with general weakness and a feeling of exhaustion appearing at the onset of the disease together with perspiration. Neither breakdown nor weakness are encountered at the beginning of the pain attack in cholelithiasis. Pain but not weakness prevails in the clinical picture. It may even be considered that the severity of the condition in acute cholecystitis corresponds with the degree of the inflammation in the region of the gall bladder, i.e. intensity of pain and muscle rigidity, fever, and leucocytosis. A patient with myocardial infarction, in contrast, gives the impression that his condition is graver despite the absence of signs of muscle rigidity.

Information on the character of the referred pain is of invaluable significance. Examination repeated sometimes 30 minutes or one hour later reveals that a patient with myocardial infarction, besides the hypochondriac pain found earlier, has also pain in the chest, neck, arms, or the left upper limb. In some cases the force of the first cardiac sound changes within that time, the cardiac rhythm is impaired or the arterial pressure falls sharply.

Unbearable abdominal pain is usually observed in extensive myocardial infarction which is marked by characteristic ECG changes and increased activity of specific blood serum enzymes as a rule. The ECG signs of myocardial infarction appear usually a few hours after the beginning of the pain attack. A series of ECG show the sequence of changes in the *ST-T* segment characteristic of myocardial infarction. Blood serum creatine phosphokinase activity begins increasing four to six hours after the onset of the pain and reaches its peak in the first 24 hours of the disease. The activity of aspartate aminotransferase increases somewhat later. Repeated recording of the ECG and repeated tests for enzyme activity, particularly the MB fraction of creatine phosphokinase contained only in the myocardium, make differential diagnosis between myocardial infarction and calculous cholecystitis much easier.

Perforation of a hollow organ. Abdominal pain in myocardial infarction is sometimes attended with marked rigidity of the abdominal wall. A sharp drop of arterial pressure with simultaneous appearance of peripheral signs of shock may be interpreted erroneously as consequences of acute abdomen occurring in perforation of an ulcer of the stomach or some other hollow organ. Errors of this kind are very rare but they may be completely avoided if it is borne in mind that the abdomen is often distended in myocardial infarction but characteristically drawn in in perforation of an ulcer. Rigidity of the abdominal wall in a patient with infarction is usual-

ly inconstant: it diminishes or disappears completely when the patient's attention is diverted. In the case of a perforated ulcer distraction of the patient's attention does not affect the intensity of muscle rigidity. A patient with peritonitis lies still in bed from the very onset because each movement intensifies the abdominal pain. Abdominal pain in a patient with myocardial infarction does not alter in intensity with changes in the patient's position in bed.

The appearance of retrosternal pain or spread of the pain to the chest and upper limbs, as well as tachycardia and marked disorders of cardiac rhythm (cardiac fibrillation, paroxysmal tachycardia, atrioventricular block) in the initial period of the disease or typical changes on the ECG are evidence in favour of myocardial infarction. The disappearance of hepatic dullness and the presence of air in the abdominal cavity allow perforated ulcer to be diagnosed.

Acute pancreatitis. A clinical picture of myocardial infarction with abdominal pain closely resembles the picture of acute pancreatitis. This is explained both by the similarity of the principal clinical manifestations of both diseases and the possibility of these diseases developing in the patient at the same time.

Necrosis of the pancreas leads to the appearance of proteolytic enzymes in the blood under the effect of which focal necroses may form in the myocardium; acute pancreatitis develops in some cases and causes painful sensations in the region of the heart and, probably, disorders of conduction and cardiac rhythm.

Pain and shock may be equally pronounced in both diseases. The fear of death and general anxiety are frequent signs of acute pancreatitis. The same symptoms are characteristic of myocardial infarction too. Pain in the upper abdomen, which is referred to the left upper limb, left shoulder, left shoulder blade or the interscapular area is considered characteristic of acute pancreatitis. Such localization of pain is encountered in approximately 5 per cent of patients with myocardial infarction. The retrosternal pain typical of infarction occurs sometimes in pancreatitis too. Moreover, since in these two diseases the laboratory tests often yield similar results, it is obvious that the differential diagnosis between them is mainly founded on the physician's skill in appraising the nuances of the identical symptoms.

Pain in pancreatitis appears sharply and is permanent. Myocardial infarction is marked by wave-like intensification of pain. In pancreatitis pain in the epigastrium is felt for a long time. In uncomplicated myocardial infarction pain lasts for only a few hours. Pancreatitis is usually attended with signs of gastric and intestinal paresis and more or less pronounced meteorism. Repeated vomiting in a patient with myocardial infarction is most frequently consequent upon concomitant pancreatitis.

Acute necrosis of the pancreas is complicated by shock as a rule.

A sharp fall of arterial pressure may be among the causes of coronary insufficiency the ECG signs of which (depression of the *S-T* segment, appearance of a negative or diphasic *T* wave in one or more leads) are found in approximately half of patients with pancreatitis. Such signs remain for a relatively short time in cases with serous pancreatitis but may persist for several weeks in necrosis of the pancreas. Evolution of ECG changes which is typical of myocardial infarction is usually not observed in pancreatitis.

The results of tests for the activity of pancreatic enzymes also help little in making the differential diagnosis between acute pancreatitis and myocardial infarction. Blood amylase and urinary diastase activity increases not only in pancreatitis but in pneumonia, perforated gastric ulcer, and other acute diseases of the abdominal organs. The activity of these enzymes intensifies noticeably under the effect of morphine, pantopon, and other drugs constantly used in the management of myocardial infarction.

Clinical experience shows, however, that urinary diastase activity of over 512 units is evidence of acute pancreatitis that has developed as an independent disease or concomitantly with myocardial infarction. It should be emphasized that normal diastase activity does not rule out the diagnosis of acute haemorrhagic pancreatitis.

The results of a series of tests for the heart isoenzyme creatine phosphokinase (CPK) make the differential diagnosis between myocardial infarction and acute pancreatitis much easier. The activity of this fraction in blood serum begins increasing in the first hours of myocardial infarction and remains above normal level for four to five days. In all other diseases, with the exception of myocardial infarction, the activity of this fraction does not change. It is particularly advisable to test CPK activity when the ECG changes are not sufficiently specific. Such situations are often encountered in patients with a history of myocardial infarction or with left or right bundle branch block.

The results of echocardiography may also help greatly in cases in which the diagnosis proves difficult. The contractile activity of the myocardium hardly changes in pancreatitis. In myocardial infarction, in contrast, the echocardiogram demonstrates zones of akinesia, hypokinesia, and paradoxical movements of the interventricular septum or left ventricular wall. The signs listed are of differential diagnostic importance in patients with bundle branch block but are insufficiently convincing in those with second infarction.

Clinical experience shows that the diagnostic difficulties can usually be solved by watching the course followed by the disease and the sequence and evolution of each symptom. Particular attention should be focused on serious disorders of the cardiac rhythm, namely, frequent polytopic extrasystoles, cardiac fibrillation, supraventricular tachycardia, and disorders of atrioventricular conduction. These

disorders of cardiac rhythm are often short-lived but their appearance should always be accepted as an argument in favour of myocardial infarction. Slowly growing signs of peritoneal irritation, persistent vomiting, spread of pain in the left half of the abdomen (along the distribution of the left splanchnic nerve), and high position of the left half of the diaphragm are only encountered in pancreatitis.

Acute Right-Ventricular Failure

Acute development of right-ventricular failure is attended with severe pain in the right hypochondrium, which may be attributed erroneously to acute cholecystitis. We observed acute right-ventricular failure with sharp pain in the right hypochondrium in patients with mitral stenosis complicated either by the tachycarditic form of cardiac fibrillation or by paroxysmal tachycardia. All these patients were unaware of the heart disease and applied for the first time for medical advice because of the sudden sharp pain in the right hypochondrium. This pain may evidently be attributed to stretching of the Glisson's capsule by the sharply enlarged liver. The pain in the right hypochondrium may be so intense that exploratory laparotomy is performed on the patient because acute cholecystitis is suspected.

The diagnostic error may be avoided if it is borne in mind that palpation reveals enlargement not only of the left but also of the right lobe of the liver in these patients. The right lobe is sometimes enlarged even more considerably than the left. Both lobes are equally tender to palpation in right-ventricular failure, whereas in acute cholecystitis tenderness is mainly elicited in the region of the gall bladder. Body temperature and the blood leucocyte count are normal in acute right-ventricular failure in the absence of concomitant diseases but increased in cholecystitis.

Tachycardia makes detection of cardiac fibrillation very difficult. Heart murmurs characteristic of mitral stenosis are not heard as a rule when the rate of cardiac contractions is approximately 150 per minute. The irregularity in the intervals between some of the contractions is so reduced that it is usually not caught by auscultation. Cardiac fibrillation is suspected in these patients because of the altered intensity of the first heart sound. The ECG demonstrates the well known signs of cardiac fibrillation and hypertrophy of the right heart.

In addition to pain in the right hypochondrium, such patients suffer from severe dyspnoea changing to orthopnoea and have a moderate or great amount of moist, usually fine bubbling rales due to blood stasis in the lungs. The signs of peritoneal irritation are mild and do not grow in the period of observation. Rapid digitalization

results in noticeable abatement of tachycardia, dyspnoea and pain in four to five hours. Digitalization for in-patients is performed by intravenous infusion of digitoxin preparations. Other cardiac glycosides prove to be much less effective in such situations as a rule.

It is our experience that the main differential diagnostic signs which allow acute right-ventricular failure to be distinguished from acute cholecystitis are as follows: cardiac fibrillation, dyspnoea, normal body temperature, tachycardia the severity of which is out of proportion to the severity of the local symptoms, and the absence of leucocytosis and progressive intensification of the signs of peritoneal irritation.

Pericarditis with Effusion

Many authors point to the appearance of sharp pain in the epigastrium in pericarditis with effusion. It is our experience that such pain arises only when a large amount of fluid is collected in the pericardial sac. The true cause of the epigastric pain in such cases becomes obvious after routine clinical examination which discloses sharply pronounced signs of heart block caused by the pericardial effusion in all patients. The pain develops simultaneously with the collection of fluid in the pericardial cavity. In all cases in our experience the whole liver was tender to palpation. No signs of acute abdomen were encountered in the patients.

Massive Necrosis of the Liver

Moderate or very intensive abdominal pain may occur in the prodromal period of acute virus hepatitis. It is also encountered in rare cases in exacerbation of chronic hepatitis. Fresh necroses of the hepatic tissue are found on postmortem examination in all such cases. The pain in the prodromal period of virus hepatitis may occur in paroxysms or may be continuous with bouts of intensification. At the peak of the pain the patient may vomit once or repeatedly. The pain is localized in the epigastrium and is felt for about 24 hours after which it abates and disappears by the end of the second or third day. After the pain ceases, mild jaundice and moderate enlargement of the liver and spleen are detected. An enlarged gall bladder is sometimes palpated.

Pain in exacerbation of chronic hepatitis is usually felt in the entire abdomen. It is usually continuous and intensifies from time to time. Sometimes it is unbearable. Marked abdominal distension was found in all our patients. The anterior abdominal wall was very tender to palpation but its rigidity was not constant. Signs of peri-

toneal irritation were not pronounced and peristalsis was preserved. Pain preceding jaundice was sometimes taken for a manifestation of a surgical disease of the abdominal organs, usually appendicitis or ileus.

Abdominal pain in fresh necrosis of the liver, as distinct from that in ileus, is not attended with intensified peristalsis. Vomiting in hepatic necrosis may be repeated but it is never the principal syndrome in the clinical picture and never has the character of intestinal (faecal) vomit. Body temperature is often elevated at the onset of necrosis of the liver. Toxicosis in this disease is pronounced from the beginning, whereas ileus is marked by growth of toxicosis during the process. Signs of functional deficiency of the liver are of decisive importance; these are increased activity of blood transferases, positive hepatic precipitation tests, increased concentration of bilirubin in blood.

It is much more difficult to distinguish abdominal pain in fresh liver necrosis from pain in appendicitis. When considering the differential diagnosis between these diseases, one should firstly take into account the medical history. The prodromal period of virus hepatitis is often marked by arthralgia, catarrh of the upper respiratory tract, diarrhoea, and sharply pronounced weakness. The patient never had any of these signs and symptoms in the past.

Some patients with appendicitis note that they had suffered a similar attack of pain before. Pain in appendicitis, though attended with vomiting, arises in the region of the umbilicus or in the epigastrium but is later concentrated in the right iliac region and becomes continuous. We did not encounter such migration of pain with a change in its character in necrosis of the liver. The gradual intensification of peritoneal phenomena in the iliac region so characteristic of appendicitis never happens in necrosis of the liver. Abdominal distension occurs at the onset of the pain in necrosis of the liver; in appendicitis the abdomen is distended only if peritonitis develops. The association of pain with necrosis of the liver must be confirmed in every case by the signs of hepatic functional deficiency listed above.

Acute Gastritis and Acute Enteritis

Abdominal pain, colicky and less frequently continuous, usually arises in an individual who takes large amounts of alcohol, eats spicy foods or nuts, takes some drugs (acetylsalicylic acid, cardiac glycosides, etc.), eats unripe apples and other fruit ('green apple colic') after eating food contaminated with staphylococci, or ba-

cilli of the paratyphus group (usually *Salmonella enteritidis* or *Salmonella suipestifer*). Acute gastritis and acute enteritis sometimes develop in idiosyncrasy and allergy to some food (e.g. strawberries, honey, mushrooms). As the result of sanitary food control carried out throughout the country, cases of gastroenteritis due to poisoning by the toxins of *Clostridium botulinum* and *Clostridium welchii* are extremely rare in the Soviet Union.

In typical cases, 4 to 24 hours after taking one of the drugs mentioned above or eating spoiled or bad food a person feels more or less weak, has a sensation of heaviness in the epigastrium and nausea. Colicky pain in the abdomen usually appears soon, in addition, followed by vomiting (once or more). Remnants of food that had been taken not long ago are often found in the vomit. The patient's condition improves noticeably after vomiting. Intestinal activity is not disturbed in acute gastritis. A loose, usually abundant stool and a splashing (succussion) sound in the caecum indicate the development of concomitant enteritis.

In mild cases vomiting occurs only once. In severer cases the patient vomits repeatedly as a consequence of which dehydration, hyponatraemia, hypokalaemia, and chlorpenia develop rapidly and are manifested clinically by general weakness, and spasms of the striated muscles. Spasms of the gastrocnemius muscles are particularly common. The abdomen is often distended. Diffuse, moderate or pronounced, tenderness is found in the epigastrium. A loud rumbling sound is often heard, sometimes even at a distance. The clinical picture in the initial stages of the disease resembles ileus in some cases and appendicitis or angina abdominis in others.

The differential diagnosis between acute enteritis (acute gastritis) and appendicitis is a most crucial and difficult problem. Both diseases often begin with vomiting and pain which is located with difficulty in the region of the umbilicus or the epigastrium. The connection of these phenomena with the intake of bad food or with a previous attack of appendicitis sometimes becomes obvious only after the final diagnosis has been established. We think that the differential diagnosis should be based on the results of routine, usually repeated, clinical examination of the patient rather than on these unreliable findings from the case record and medical history.

Both diseases begin with pain which in acute enteritis subsides markedly after a stool is passed and then disappears completely. Appendicitis is characterized by migrating pain. It is at first localized around the umbilicus or in the epigastrium, but in a few hours it moves to the right iliac region and becomes continuous here.

At the onset of the disease the abdominal wall overlying the vermiform process may be not tender at all or only mildly tender. Tenderness gradually increases characteristically in the later stages.

A few hours after the beginning of the disease the abdominal wall becomes more and more rigid and signs of peritoneal irritation appear. The Shchetkin-Blumberg sign is always negative in acute enteritis and acute gastritis.

Vomiting is particularly severe at the onset of acute gastritis but does not occur later. In appendicitis vomiting is also often encountered at the onset but soon ceases and recurs again if more or less diffuse peritonitis develops.

Body temperature is often slightly elevated in appendicitis but is usually normal in acute enteritis. A gradual increase in the pulse rate is characteristic of appendicitis but is not observed in cases with ordinary enteritis.

Auscultation of the abdomen reveals intensified peristalsis in acute gastritis (enteritis). In appendicitis peristalsis is heard only in parts of the abdomen which are remote from the caecum; over the caecum it is either sharply diminished or not heard at all.

Digital examination of the rectum is painful in appendicitis because of peritoneal irritation. This sign is encountered always when the apex of the vermiform process is found to the left of the caecum. Palpation of the rectum in acute enteritis (or acute gastritis) is always painless. Diarrhoea is encountered in approximately 18 per cent of cases with acute appendicitis: in 2.5 per cent it precedes the pain. Appendicitis should be suspected in every case of 'food poisoning' or acute gastroenteritis and rectal examination should be carried out in every aetiologically unclear case of the disease.

Gynaecological and Obstetrical Diseases

Females with acute pain in the lower abdomen are often brought to the admission department of large hospitals. If this pain has occurred for the first time and is attended neither with signs of peritoneal irritation nor with vaginal haemorrhage, the patient is sent to the internist on duty. In most cases, however, this pain is associated with rupture of the follicle, an ovarian cyst, dysmenorrhoea, acute adnexitis or extrauterine pregnancy.

Acute abdominal pain is encountered in those cases of **ovulation** which are attended with haemorrhage into the abdominal cavity. Rupture of the graafian follicle usually occurs in the middle of the menstrual cycle although under the effect of emotional and other environmental factors it may happen earlier or later than this period. Because of the blood accumulated in the Douglas' pouch, movements of the uterine neck in these patients are very painful. If analgesics and bed-rest do not relieve the pain, consultation with

a gynaecologist or surgeon is indicated because in rare cases bleeding from the follicle may be copious and can be arrested only by applying sutures.

Pain in the lower abdomen without signs of peritoneal inflammation is encountered in **acute adnexitis**. The clinical picture at the onset of the disease may resemble that in appendicitis. A diagnostic error is easily avoided if it is borne in mind that in most cases with acute adnexitis abdominal pain is attended with elevation of body temperature and pain in the small of the back but not by vomiting. At first the abdominal pain may be bilateral but later it becomes more pronounced on the right or the left side. Vaginal examination reveals tenderness of the uterine neck on movements and often bilateral or unilateral enlargement of the adnexa.

Pain in **extrauterine pregnancy** usually appears simultaneously with the bleeding but sometimes it precedes the uterine haemorrhage by 12 to 24 hours. Sometimes menstruation does not stop in which case it is very difficult to establish the diagnosis. When there is a threat of rupture of the right fallopian tube the clinical picture resembles that in acute appendicitis (with localization of the vermiform process in the true pelvis). Body temperature remains normal, the pulse rate increases. The abdominal wall is often mildly rigid but there are no marked signs of peritoneal irritation. Rupture of the tube is attended with collapse. Pain in the arm arises simultaneously with the abdominal pain if the escaping blood is collected under the diaphragm. Collection of blood in the Douglas' pouch is revealed during vaginal examination by severe tenderness of the uterine cervix on movements. Vaginal examination and exploratory puncture of the Douglas' pouch yield the most reliable information for differentiating the disease from acute appendicitis.

Dysmenorrhoea sometimes begins with acute abdominal pain arising several hours or even 24 hours before the bleeding. It is often attended with vomiting and in some cases also by collapse. The abdomen is always soft to palpation while body temperature sometimes increases to 37.5°C after ovulation. Sharp pain in the lower abdomen may be consequent upon haemorrhage into an ovarian cyst or torsion of the ovarian pedicle. In the latter case, the patient often faints during the attack of pain. A uni- or bilateral tumour is found by bimanual examination. Rupture of a cyst is accompanied with peritonitis but not 'pseudoacute abdomen' that is encountered in the practice of an internist.

Abdominal Angina

Individuals over 70 years of age often apply to a physician because of colicky pain in the abdomen arising soon after a meal and

ceasing soon after a loose and usually abundant stool has been passed. The development of this pain is linked with temporary deficiency in the blood supply to the intestine because of atherosclerosis, mainly of the superior mesenteric artery. The pain is usually felt in the region of the umbilicus. In other cases with abdominal angina the pain in the abdomen is attended with drastically intensified production of gases. A great amount of gases is passed in most cases of diarrhoea. Pains in the heart and in the left upper limb are felt in rare cases at the same time as the abdominal pain. Nitroglycerin relieves the pain in the abdomen noticeably or even completely.

On account of the connection of the pain with eating and diarrhoea, attacks of abdominal angina are often mistaken for acute enteritis. A correct diagnosis can be established only after long-term observation over the patient, his dietetic habits, and the character of reaction to medication with vasodilators. Attacks of abdominal angina sometimes become more frequent shortly before thrombosis of branches of the superior mesenteric artery.

Acute Porphyria

Abdominal pain in impaired porphyrin metabolism may be so intensive that exploratory laparotomy is performed on the patient sometimes. Acute disorders of porphyrin metabolism may be roughly divided into congenital and acquired. Hereditary diseases usually encountered in different generations of one family are related to porphyria proper. Abdominal pain is particularly characteristic of acute intermittent porphyria, which is very rare in the Soviet Union. Females are affected more frequently than males.

The disease usually sets in between the ages of 20 and 30 and is manifested by attacks of colicky pain in the abdomen. Spasm of the smooth muscles of the intestinal wall or stomach is the cause of the pain. Colicky pain in the region of the umbilicus may be the principal or even the only manifestation at the beginning of the disease. The spasmodic intestinal segment is often mistaken for a tumour and serves as a reason for laparotomy. Sometimes the abdominal colic is paralleled by spasm of the central artery of the retina with the development of temporary amaurosis. The colicky abdominal pain is often attended with vomiting. The colic is usually preceded by severe constipation. Leucocytosis, moderate fever, and increased arterial pressure are often encountered during the abdominal crisis.

In patients with recurrent abdominal crises, symptoms of affection of the nervous system appear in addition to the clinical picture described above. Psychic disorders (delusions, hallucinations, epileptic seizures) sometimes develop. Polyneuritis occurs much

earlier and more frequently. Affection of the extensors of the hands and feet is accepted as a characteristic symptom. Bulbar disorders occur in later stages of the disease. Involvement of the muscles of respiration may result in marked respiratory insufficiency.

An increased content of porphyrins is found in the patient's urine during the attack of abdominal pain. Only traces of them are present in the urine of a healthy person. When their content exceeds 1 ml/24 hours the urine becomes coloured. In typical cases, freshly voided urine has the colour of port wine. Less frequently it is pink or red because a red zinc-porphyrin complex is produced. In some cases, the freshly voided urine contains colourless precursors of porphyrin, namely, porphobilinogen or delta-aminolaevulinic acid. When the urine is left in the sunlight these colourless compounds are converted to porphyrin. Excretion of normally coloured urine does not rule out porphyrinuria and in cases with suspected acute porphyria the urine must therefore be sent to the laboratory for special tests for porphyrins.

Increased sensitivity of the skin to light is detected in some patients at the time of the abdominal colic. Insolation causes erythema, pruritus, and then vesicles ('hydroa aestivale') in these patients. In some forms of porphyria, the teeth have a pinkish tinge and exhibit red fluorescence in ultraviolet light. Attacks of abdominal colic are encountered in patients with normal and in those with abnormally high sensitivity to light. Hypersensitivity to light, polyneuritis, and a red urine allow an attack of acute intermittent porphyria to be differentiated from acute abdomen.

Excretion of porphyrin in the urine and faeces increases under the effect of some drugs. Disorders of porphyrin metabolism are particularly pronounced after medication with Sedormid (Apronal), sulphanilamides, barbiturates, griseofulvin, preparations of arsenic, phosphorus, selenim, and lead and after alcohol. When the clinical signs of porphyria appear after small doses of the drugs listed, it may always be assumed that the drug had simply activated an existing latent porphyria.

Crohn's Disease

In approximately 20 per cent of cases Crohn's disease is mistaken for appendicitis on the first examination of the patient. This is explained by the fact that the pathological process in Crohn's disease is usually localized in the terminal segment of the ileum. All the coats of the affected intestine are involved in the granulomatous inflammatory process. Its wall is considerably thickened. Enlarged lymph nodes appear in the thickened mesentery. Spread of the inflammatory process to the parietal peritoneum gives rise to pain

which is usually localized in the right iliac region. When this pain is accompanied with symptoms of peritoneal irritation and moderate leucocytosis, the diagnosis of acute appendicitis seems most probable and exploratory laparotomy is undertaken.

In many cases exploratory laparotomy proves necessary because it allows a competent surgeon not only to prevent the development of peritonitis but to establish the correct diagnosis. The wall of the affected areas of the ileum or colon is noticeably thickened and its serous surface is sharply hyperaemic. Some of the loops of the small intestine often adhere to one another or to the adjacent areas of the colon. The affected intestinal segment is stenosed, while the segment proximal to the site of the stenosis is dilated.

If the pain in the right iliac region is not attended with peritoneal phenomena, the diagnosis of Crohn's disease may be made without resorting to exploratory laparotomy. In considering the differential diagnosis between acute appendicitis and Crohn's disease it is necessary first of all to appraise the medical history and case record thoroughly. In Crohn's disease, abdominal pain joins diarrhoea the duration of which in some patients ranges from several days to several years. Sometimes it can be disclosed that periods of diarrhoea are replaced by periods with a normal stool. Diarrhoea is a very rare symptom in acute appendicitis, but if it occurs, then only at the onset of the disease but not preceding it by a few days or weeks.

Vomiting occurring once or repeatedly is among the common symptoms of acute appendicitis. In Crohn's disease with pain in the right iliac region, vomiting is a very rare occurrence. Pain in appendicitis often appears first in the region of the umbilicus and later migrates first to the epigastrium and then to the right iliac region. Only here it becomes persistent and is attended with rigidity of the abdominal wall and peritoneal phenomena. Acute appendicitis is characterized by growth of leucocytosis, gradual elevation of body temperature, and increase in the pulse rate. In Crohn's disease the pain and fever are less marked than those in acute appendicitis and no migration of pain in the abdomen is encountered. Leucocytosis usually does not grow during the period of observation, while the rate of cardiac contractions does not change.

Acute Mesadenitis and Acute Ileitis

The clinical picture of mesadenitis comprises symptoms of the principal disease and local signs of inflammation of the mesenteric lymph nodes and the adjoining peritoneum. In most cases the dis-

ease takes a chronic course though an acute course may be encountered in rare cases. Abdominal pain may be moderate or very intense. It is usually localized in the umbilical or right iliac region and much less frequently in other parts of the abdomen. Abdominal distension and moderate or high fever are often observed at the same time as the pain. Sharp colicky pain usually lasts about two or three hours and then abates gradually. In a few cases intensive pain persists for one or two days.

Depending on the localization of the pain, tuberculous mesadenitis has to be most frequently distinguished from appendicitis and pancreatitis. The clinical picture of acute mesadenitis and acute terminal ileitis caused by *Yersinia enterocolitica* is usually mistaken for that of acute appendicitis or Crohn's disease (Sjöström, 1971). Acute or chronic mesadenitis is a very difficult diagnostic problem. In some cases the final diagnosis can be established only from the results of bacteriological examination of material removed during operation. The clinical diagnosis of tuberculous mesadenitis, though difficult, is nevertheless possible.

In considering the differential diagnosis of tuberculous mesadenitis and acute appendicitis attention should be first of all focused on the onset of the disease. Acute appendicitis occurs suddenly in full health. Tuberculous mesadenitis develops usually in a person with sufficiently pronounced tuberculous toxicosis manifested by loss of appetite, frequent headache, subfebrile temperature, diminished capacity for work, increased ESR, and sometimes by anaemia. The pain in appendicitis usually arises in the epigastrium and moves later to the right iliac region. Such characteristic migration of pain is not encountered in tuberculous mesadenitis; in this disease it is always felt in one and the same region.

In tuberculous mesadenitis the abdominal wall, though tender, participates in the act of respiration and is rarely rigid. The Shchetkin-Blumberg sign is usually weakly positive and does not change in intensity with time. Enlarged lymph nodes of a firm consistency are sometimes found on deep palpation in the right iliac region. Radiographs of the abdominal cavity may demonstrate foci of calcification along the line of the attachment of the mesentery.

Abdominal distension in acute appendicitis is caused by peritonitis and develops only in the late stage of the disease. Distension of the abdomen and retention of gases in tuberculous mesadenitis are due to partial intestinal obstruction and are usually encountered at the beginning of the pain. Growth of leucocytosis and rate of cardiac contractions is characteristic of acute appendicitis. These signs are usually not observed in tuberculous mesadenitis.

In making the differential diagnosis between tuberculous mesadenitis and pancreatitis one should take into account that in acute pancreatitis pain appears in full health, whereas pain in mesade-

nitis always develops in an individual with long existing symptoms of more or less pronounced tuberculous toxicosis.

The very intense pain in acute pancreatitis is referred to the left side or is of the girdle type. Pain in the epigastrium and middle abdomen in tuberculous mesadenitis is never as intense as the pain in pancreatitis. Pain in mesadenitis is never attended with disorders of pancreatic external secretion. The content of diastase and amylase in blood and urine remains normal.

Acute inflammation of the lymph nodes of the distal segment of the ileum caused by *Yersinia enterocolitica* is usually attended with diarrhoea and is mistaken for appendicitis. The true cause of the 'appendicitis with diarrhoea' remains unclear even after operation and histological examination of the removed organ. The aetiology of the disease may be established only after special bacteriological studies.

Periodical Disease (Familial Mediterranean Fever)

Acute pain in the abdomen is usually the earliest and almost constant symptom of the abdominal variant of periodical disease. The pain results from benign paroxysmal peritonitis. The disease is often familial and usually begins in childhood. It is most frequently encountered among boys of Jewish, Arabian, and Armenian origin. The attack of abdominal pain is usually preceded by indisposition, loss of appetite, arthralgia, and impaired intestinal activity. Growing gradually, these phenomena are replaced by abdominal pain usually localized in the right abdomen or epigastrium. Fever develops at the same time as the pain. Body temperature rises to 38-40°C with a chill and remains so for several hours or one or two days and then gradually drops to normal. Like in other cases with inflammation of the peritoneum, the patient with benign peritonitis prefers to lie still in bed.

Vomiting, sometimes repeated, occurs at the peak of the pain which may be colicky or continuous. The abdomen is usually distended, the face hyperaemic, and the abdominal wall rigid and sharply tender to palpation. Hepatomegaly is a frequent finding. Splenomegaly is encountered much less frequently. Leucocytosis and increased ESR are found in all cases. Signs of partial intestinal obstruction appear at the peak of the attack, but they usually do not predominate in the picture of the attack and do not tend to advance.

Dynamic intestinal obstruction in an uncomplicated attack of periodical disease differs from intestinal obstruction which calls

for surgery by the presence of more or less pronounced peritoneal signs from the onset of the disease, fever, and frequent appearance of pain in the joints and chest, in addition to the abdominal pain. Peristalsis which is drastically intensified at the beginning of periodical disease is much less pronounced at the peak of the attack. The passage of gases indicates the end of the attack.

Particularly difficult diagnostic problems are encountered during the first attack of benign paroxysmal peritonitis. The appearance of symptoms of peritoneal irritation soon after the pain arises prompts the physician to resort to surgery. The erroneous diagnosis of appendicitis is made especially often and appendectomy is performed. The correct diagnosis is established more easily in recurrent attacks because of the stereotyped clinical picture. Information on the patient's nationality and the existence of similar diseases among relatives is of great value. High fever and marked leucocytosis are manifest in the first hours of an attack of paroxysmal peritonitis, which never happens in acute appendicitis.

In some cases of periodical disease, fever develops at the same time as the attack of sharp pain in the right hypochondrium and the sclera and skin become slightly jaundiced, which Vinogradova (1973) attributes mainly to dyskinesia of the biliary tract. Leucocytosis and symptoms of peritoneal irritation add to the similarity to acute cholecystitis. Periodical disease with an attack of sharp pain in the right hypochondrium differs from acute cholecystitis in the systemic character of the developing functional disorders.

Signs of affection of other organs and systems are always detected at the time of the hypochondriac pain in periodical disease. Arthralgia (sometimes with no noticeable change in the shape of the joint) and polyarthritis are particularly common. Much less frequently pain in the right hypochondrium is attended with dysuria, chest pain, and sometimes with symptoms of pleurisy. Such combinations are not characteristic of ordinary acute cholecystitis.

Haemorrhagic Vasculitis

Acute abdominal pain may be the first clinical manifestation of haemorrhagic vasculitis attacking males, usually in childhood and adolescence. In most cases with this disease, haemorrhagic eruption appears simultaneously on the skin and on the wall of the small intestine. Isolated affection of the vessels of the intestinal wall is rarely encountered. Depending on the severity of this process, either diarrhoea or signs of dynamic intestinal obstruction with repeated vomiting develop. Symptoms of peritoneal irritation are usually absent or very mild.

Haemorrhagic vasculitis commonly sets in with purpura and poly-

arthritis. Purpura is usually localized on the extensor surface of the lower limbs and on the lower abdomen. The articular syndrome is manifested by sharp pain in the large and less frequently the small joints of the lower limbs and often by periarticular swelling. The joints of the upper limbs are involved much less frequently. Moderate fever, leucocytosis, and increased ESR contribute to the picture. Symptoms of glomerulonephritis appear in later stages of the disease.

More or less severe phenomena of intestinal obstruction develop almost in every case of haemorrhagic vasculitis. Their severity and the need for surgical intervention are determined by the extent of involvement of the intestinal wall and the degree of impairment of its motor function. In most cases the disease follows a course without the development of a progressive picture of ileus. The absence of symptoms of peritoneal irritation at the onset distinguishes haemorrhagic vasculitis from perforating ulcer of the stomach. Vasculitis of the terminal ileal segment is marked by pain in the right iliac region or even in the entire right half of the abdomen. A tentative diagnosis of acute appendicitis is sometimes made in such cases.

Inflammation of a retrocaecal vermiform process produces no signs of peritoneal irritation for some time. The differential diagnosis in such instances should be based on the results of dynamic observation of the sequence and severity of the other symptoms of the diseases that are compared.

If signs of peritoneal irritation appear during the period of observation and if they begin intensifying surgery is indicated even in a patient with an obvious diagnosis of haemorrhagic vasculitis.

Acute Diabetic Abdomen

Acute infectious diseases, injuries, and emotional shock often lead to exacerbation of all manifestations of diabetes mellitus. The patient's condition sharply deteriorates. In some cases a precomatose state develops because the patient refuses an insulin injection. The patient feels weak at first and then the weakness progresses, as a result of which headache, nausea, vomiting and somnolence develop. Breathing becomes deeper gradually, the skin and mucous membranes become dry, and thirst and polyuria appear. Vomiting recurs and the vomit is sometimes bloody because of diapedetic haemorrhage.

Such patients are often brought to a surgical department with the diagnosis of acute appendicitis, acute cholecystitis or intestinal obstruction. It is presumed that the pain and signs of peritoneal irritation in these patients arise either as a consequence of increas-

ing dehydration of the peritoneum or as the result of punctate extravasations into the peritoneum and pancreatic tissue. Peritoneal phenomena and abdominal pain consequent upon diabetic acidosis subside noticeably two or three hours after the patient recovers from the state of diabetic precoma. If they do not subside, the diagnosis must be reconsidered.

Acute diabetic abdomen always develops gradually. Examination of the patient reveals easily dyspnoea, acetone odour in the breath, glucosuria, ketonuria, and hyperglycaemia. Acute diabetic abdomen always begins with exacerbation of diabetes in addition to which abdominal pain and vomiting develop later. The condition must be distinguished from true acute abdomen in a diabetic patient. In a patient with diabetes, acute appendicitis or acute cholecystitis also sets in with pain in the abdomen and vomiting. The difference consists in the pain and vomiting occurring in full health in an individual with completely controlled diabetes. Therapeutic measures aimed at relieving diabetic acidosis have absolutely no effect on the manifestations of appendicitis or cholecystitis. The medical history, the results of repeated examination of the patient, and in the late stages also the results of trial therapy make it possible to establish the correct diagnosis.

Renal Colic

Acute renal colic sometimes produces a clinical picture which may be very easily mistaken for that of appendicitis, ileus, biliary colic or pancreatitis. An attack of renal colic occurs suddenly. The colicky pain may be felt over the entire abdomen or only in one of its halves and is usually attended with vomiting and abdominal distension. In typical cases it is referred to the groin and accompanied with dysuria. Reflex anuria occurs sometimes. During the attack the patient changes his position in bed many times, which in some cases relieves the pain a little for a short while.

Right renal colic most commonly has to be differentiated from acute appendicitis which may also begin with vomiting and pain in the right abdomen. Many authors claim haematuria to be a reliable sign distinguishing these two diseases from each other. Unfortunately, one cannot agree with this point of view. True, renal colic is complicated by haematuria in 80 to 90 per cent of cases, but haematuria is also often encountered in retrocaecal appendicitis. This form of appendicitis is rare, but the physician always has to make the diagnosis in one concrete patient and statistical data therefore cannot be of decisive significance. Reflex anuria is a rare attendant condition in renal colic, but it is also rarely encountered in appendicitis.

In considering the differential diagnosis between these two diseases, it is advisable to pay attention to the patient's behaviour in bed, which is closely connected with the specific features of the development of the pain.

In approximately 93 per cent of cases, appendicitis sets in with abdominal pain which is at first felt in the middle of the abdomen (periumbilical) or in the epigastrium. Vomiting occurs at this time, usually with no preceding nausea. A patient with mild appendicitis vomits once. Vomiting recurring many times is characteristic of destructive appendicitis. In appendicitis, vomiting occurs, whether once or many times, in attendance to pain at the onset of the disease.

Pain in appendicitis shifts to the right iliac region a few hours after the beginning of the disease. Here it remains stable and is well localized. It intensifies markedly on movements, that is why the patient prefers to lie quietly in bed.

Thus, appendicitis is characterized by migration of pain which then becomes stable and in approximately 80 per cent of cases is typically localized in the right iliac region. In retrocaecal position of the vermiform process (in approximately 10 per cent of all patients) maximum pain is felt not in McBurney's point but in the flank of the abdomen, in a point approximately on the middle of the line between the superior anterior iliac spine and the gall bladder. A retrocaecal vermiform process is found next to the right ureter. Involvement of the latter in the pathological process leads to the appearance of red blood cells in the urine (which, as it is generally known, is a frequent occurrence in destructive forms of appendicitis) and may change noticeably the whole clinical picture of the disease.

The characteristic features of the pain help in distinguishing this type of appendicitis from right renal colic in diagnostically easy cases, whereas the results of urological examination help in cases in which the diagnosis proves difficult.

In most cases of renal colic, the pain appears in attacks. It occurs suddenly and ceases just as suddenly. It should be borne in mind, however, that pain arising from the ureter is rarely colicky in character (Jones, 1974). Like in appendicitis, it may be continuous. It is characteristically referred to the groin, testicle or the vagina. Sometimes the pain is radiated to the ileal region. The attacks of pain are often attended with nausea and vomiting. During an attack of renal colic the patient changes his position in bed actively, which is not encountered in appendicitis. Examination of urine collected during a colic reveals haematuria and in about 80 per cent of cases oxaluria. Anuria develops sometimes during a colic. If the urine is infected, its retention is attended with fever and recurrent chill.

Excretory urography or chromocystoscopy is recommended in cases

which present a diagnostic problem. In renal colic, the function of the affected kidney is either sharply inhibited or is not demonstrated. In such cases radiographs are taken every one to three hours during 24 hours. Despite anuria, the nephrogram is gradually demonstrated on the affected side and the renal pelvis and ureter become contrasted.

A nephrogram and the subsequent appearance of a pyelogram make it possible, therefore, to establish the diagnosis of renal colic with stoppage of urine outflow. A procaine block of the spermatic cord relieves pain in renal colic noticeably in some cases but is ineffective in appendicitis.

Other Diseases

Abdominal pain is sometimes the first clinical manifestation of **tuberculosis** or **tumour of the vertebrae**. Strictly localized tenderness over the affected vertebra appears long before deformity of the spine develops. Radiography of the spine is the most reliable method for the diagnosis of these diseases and the abdominal pain associated with them.

Acute abdominal pain proves to be the predominant symptom in some cases of **tabes dorsalis**. Typical abdominal crises are replaced with time by diffuse pain in the abdomen. This pain is mostly localized in the umbilical region. Severe pain and recurrent vomiting usually remain for several days. So as not to miss the true cause of the pain and to avoid unnecessary operation, it is advisable to detect the presence of characteristic shooting pain, test the pupillary and tendon reflexes, and perform the Wassermann reaction.

Severe colicky abdominal pain is encountered in **lead poisoning** and is sometimes the patient's main complaint. Scrupulous examination yields information on constipation, increased arterial pressure, and signs of lead polyneuritis in which the extensors of the wrists and fingers are involved earliest. Anaemia and increased number of sideroblasts in the blood are found. Patients with mild poisoning have signs of the asthenic syndrome. Psychoses and epileptiform seizures develop in graver cases.

Abdominal pain may be incident to **aneurysm of the abdominal aorta** which almost in all cases forms distal to the origin of the renal arteries. The pain is caused either by stimulation of the periosteum of vertebrae adjacent to the growing aneurysm or by stimulation of the spinal nerve roots. Lumbar pain is felt simultaneously. In our experience, chronic aneurysms of the abdominal aorta contained parietal thrombi. Some of them were palpated as hard rounded immobile and non-pulsating tumours. Calcification of the walls was demonstrated on the radiographs.

Rupture of the aneurysm usually occurs in several stages. In typical cases pain appears in a patient with an asymptomatic aneurysm and remains moderate for some time. A few days before the rupture, the pain in the abdomen and small of the back or the sacrum intensifies. It is referred to the groin and lower limbs. Growing in intensity with each day the pain becomes unbearable and then suddenly disappears or abates sharply. This is possibly associated with temporary cessation of the bleeding through the aortic wall. Full rupture of the aortic wall occurs later and causes sudden death from retroperitoneal haemorrhage.

The wave-like intensification and abatement of abdominal and lumbar pains with the characteristic radiation to the groin and lower limbs resembles the picture of renal colic. The correct diagnosis may be established in the period of the threatening rupture. Radiographs of the abdominal cavity taken after the bleeding has already begun may show no shadow of the iliopsoas muscle. A timely diagnosis may be established only from the results of aortography the performance of which is recommended in every case with abdominal pain of unrecognized origin.

Supplement I-1

Causes of Acute Abdominal Pain

1. Diseases of the lungs and pleura.
2. Diseases of the heart.
   - Abdominal syndrome in myocardial infarction.
   - Acute right-ventricular failure.
   - Acute pericarditis.
3. Hepatic colic and acute cholecystitis.
4. Acute pancreatitis.
5. Massive necrosis of the liver.
6. Acute gastritis and acute enteritis.
7. Abdominal angina.
8. Acute porphyria.
9. Crohn's disease.
10. Acute mesadenitis and acute ileitis.
11. Periodical disease.
12. Haemorrhagic vasculitis.
13. Acute diabetic abdomen.
14. Renal colic.
15. Other diseases.
    - Tuberculosis or tumour of the vertebrae.
    - Tabes dorsalis.
    - Lead poisoning.
    - Aneurysm of the abdominal aorta.

Chapter II

Anaemias

Anaemia is a clinical entity resulting from a decrease in haemoglobin and red cells, or in each separately, in the blood. The aetiology and mechanisms of the development of anaemias are diverse and all attempts made to classify them to date have proved to be unsatisfactory. The aetiological classification of anaemias fails to answer the purposes of differential diagnosis because in many cases the direct cause of anaemia is only illusory. For instance, the severity and clinical course of anaemia in chronic blood loss are determined not as much by the blood loss itself, as by the character of the principal disease complicated by haemorrhage. Anaemias consequent upon chronic blood loss in carcinoma of the colon, cirrhosis of the liver, and simple haemorrhoids can be grouped together neither by a common method of diagnosis, nor by prognosis nor by methods of treatment.

The widely used classification of anaemias according to the morphology of the red blood cells also fails to measure up to the requirements of differential diagnosis. The same disease sometimes leads to the development of normocytic and sometimes to macrocytic anaemia. The action of the same cause may be complicated in some cases by macrocytic and in others by microcytic or hypochromic anaemia. In prewar times, the morphological classification was based on the diameter of the red cell and the degree of its saturation with haemoglobin. With time it became apparent, however, that it would be more convenient to go by determining the volume of the red cell. The haemoglobin concentration in a normocyte always exceeds 30 per cent, while the volume of the normocyte ranges from 80 to 94 μm^3.

The mechanisms of the development of anaemias have not been sufficiently studied. This makes it difficult to use these mechanisms as the only basis for making a differential diagnosis. It is accepted that in any type of anaemia either increased destruction or reduced production of red cells occurs. The inadequacy of this viewpoint is becoming ever more apparent in recent times. Growing attention is focused on anaemias developing in patients without increased blood loss and with normal functional capacities of the bone marrow. The differential diagnosis of anaemias must therefore be based on the results of the clinical synthesis of existing classifications.

Normal erythropoiesis may take place while the body still contains sufficient reserves of vitally indispensable amino acids, iron, cobalt, copper, vitamin B_{12}, folic, ascorbic, pantothenic and nicotinic acids, pyridoxine, thiamine and, possibly, riboflavin. The lack in the diet of any of the factors listed above or disturbance of their metabolism in the body leads to the development of anaemia, which may be conventionally designated 'anaemia due to inhibition of erythropoiesis by deficiency or disturbance of the metabolism of its dietary factors' (Supplement II-1).

The functional condition of the bone marrow depends both on the factors mentioned above and on many other factors among which heredity plays a definite role. The modern physician more often encounters anaemias caused by the effect of environmental factors. Some of these are known; the action of other still unidentified factors causes the development of idiopathic anaemias. Some authors call this group of anaemias hypoplastic or aplastic, which is only partly correct, because hypoplasia of the bone marrow is encountered in most, although not in all cases of anaemias traditionally included in this group.

The mechanisms of the development of anaemias caused by acute or chronic blood loss have been studied most fully. These anaemias are widespread. Their occurrence is associated mainly with disorders of iron metabolism. Microcytosis and hypochromia are the most characteristic morphological signs of this type of anaemia. The shortened life of the red cell is the main sign of haemolytic anaemia, the acquired and congenital forms of which are usually distinguished.

Delayed Erythropoiesis due to Deficient or Disturbed Metabolism of its Dietary Factors

Deficiency of Protein in the Diet or its Increased Loss through the Gastro-intestinal Tract

Long-term delay in erythropoiesis leads to the development of more or less severe anaemia with reduced or normal number of reticulocytes. Leukopenia and thrombocytopenia often occur simultaneously with anaemia. The morphological properties of the red

cell are determined by the character of metabolic disorders. In simultaneous deficiency of folic acid and vitamin B_{12} metabolism, the volume of the red cells grows, while in disorders of iron metabolism it is below normal. A long-term diet with an insufficient protein content causes the development of anaemia even if the diet proves to be of full value in calories.

Such types of anaemia are often encountered in kwashiorkor, a frequent disease among children of Africa and Central and South America. The requirements of the body in calories in this type of anaemia are met at the cost of carbohydrates. Retarded growth and hypoalbuminaemia are encountered simultaneously with anaemia. In severer cases, hypoproteinaemic oedema and ascites develop. If the protein lack in the diet is not combined with a deficiency in vitamins and iron, the anaemia is usually normochromic and moderate. Reticulocytic crisis and haematological recovery occur in such cases only after the prescription of a diet rich in proteins.

The development of reticulocytic crisis indicates that the bone marrow functions adequately. The delay of erythropoiesis in anaemia caused by an abnormally reduced content of proteins in the diet is evidently due to insufficient stimulation of the bone marrow. If protein deficiency in the diet is attended with a lack of iron and folic acid, the anaemia is usually severe and haematological recovery in this case takes place only after the patient is given protein, iron and folic acid.

Anaemia due to protein deficiency in the body is often encountered also in adults. In patients with alimentary dystrophy, it is usually consequent upon an insufficient content of protein in the diet, in most of the other patients it results from increased loss of protein in the gastro-intestinal tract. In a healthy person, approximately 10 per cent of proteins contained in blood plasma enters the gastro-intestinal tract daily. In diseases listed in Supplement I-2, the daily loss of plasma proteins through the gastro-intestinal tract increases markedly, and in severe cases reaches 60 per cent of their total content in the vascular system. Hypoproteinaemia develops when the rate of protein loss by the body exceeds the rate of protein synthesis. This hypoproteinaemia also reflects the protein deficiency in the extravascular and intracellular spaces of the body. Protein lack in the body is among the causes of anaemia in diseases and syndromes listed in Supplement II-2. We wish to emphasize again that the protein content in the diet of these patients may be normal or even increased and the protein deficiency in the body in these diseases develops under the effect of other factors. The influence of these factors on the mechanisms of the development of iron deficiency anaemias has also been determined not long ago.

Deficiency of Vitamin B_{12} and Folic Acid or Disorders of their Metabolism

The transport to the bone marrow of factors essential for normal haemopoiesis to a great measure depends on the processes of digestion and absorption of foodstuffs, i.e. fats, proteins, carbohydrates, vitamins and electrolytes. The integral function of the gastrointestinal tract is determined by the condition of the stomach, liver, biliary tract, pancreas, the small intestine and its lymphatics and blood vessels. A more or less marked disturbance of the integral function leads to the development of the malabsorption syndrome manifested by the clinical picture of steatorrhoea, diarrhoea and vitamin and electrolyte deficiency with the corresponding clinical signs of disturbed metabolism. The detection of disturbed metabolism of iron, vitamin B_{12} and folic acid is particularly important in the differential diagnosis of anaemias.

Vitamin B_{12} deficiency. The term 'vitamin B_{12}' embraces all cobalamines and, at the same time, designates one of them used as a drug. Vitamin B_{12} (cyanocobalamine) is only contained in proteins of animal origin. The daily requirement in it does not exceed 1 μg. Negligible amounts of vitamin B_{12} are synthesized in the large intestine, but it cannot be assimilated because it is absorbed only in the distal segment of the ileum. The mechanisms of absorption have not been fully studied. It is only known that after it is freed of the dietary protein, vitamin B_{12} binds with Castle's intrinsic factor which is secreted by the parietal cells of the stomach and that this complex is absorbed on the microvilli of the ileum. Absorption occurs only in the presence of calcium salts and in neutral reaction of the medium. The binding of vitamin B_{12} with the intrinsic factor is very strong. It may be disrupted by bacterial flora.

The absorbed vitamin B_{12} enters the blood in which it binds with transcobalamines. Some of it is stored in the liver and the rest remains in the plasma and intercellular fluid from which it is consumed by the cells. Its total reserves in the body amount to approximately 4 mg. About 99 per cent of the body's requirements are provided by mechanisms of active and 1 per cent by passive absorption of vitamins.

Inability of the iliac mucosa to absorb vitamin B_{12} may be congenital (Groesbeck-Imerslund syndrome) or acquired (Supplement II-3).

The absorption of vitamin B_{12} is disturbed in diseases marked by increased acidity in the ileum, in disorders of assimilation of the dietary protein, in the consumption of the released vitamin B_{12} by bacteria or parasites inhabiting the proximal segments of the small intestine, after resection of the distal ileal segment, in involve-

ment of the ileal mucosa in a tumour, in exposure to irradiation and in inflammation. The severity of disturbance in the absorption function in radiation sickness is determined by the irradiation dose. The absorption function of the small intestine is also noticeably impaired in marked protein deficiency in the diet (e.g. in kwashiorkor) or under the effect of regular intake of alcohol and some drugs (neomycin sulphate, PAS, colchicine).

Cobalamines take part in almost all the known metabolic processes. They are essential for normal growth, haemopoiesis, maintenance of normal function of the nervous system cells and DNA synthesis in the cells. In approximately 90 per cent of cases malabsorption of these substances is determined by the inability of the gastric mucosa to secrete an enzyme known as the intrinsic factor.

This form of vitamin B_{12} deficiency has long been known to clinicists as pernicious anaemia or Addison-Biermer's disease. The same term is applied to designate anaemia caused by blocked activity of the intrinsic factor by antibodies produced against it.

Vitamin B_{12} deficiency of other origin is indistinguishable clinically from pernicious anaemia. As it is mentioned above, although its causes are numerous, it is much rarer than pernicious anaemia resulting from deficient secretion or inactivation of the intrinsic factor. Further we shall refer to all forms of vitamin B_{12} deficiency, irrespective of their origin, as pernicious anaemia purely for the sake of brevity.

In some cases the diagnosis of pernicious anaemia may be made tentatively from the patient's appearance. The most characteristic signs are grey hair and yellowish skin of a middle-aged person who complains of dizziness, dyspnoea and sharply diminished tolerance to physical exertion, paraesthesia of the extremities, and a tendency to diarrhoea. The patients usually seem well-nourished, although many of them complain of weight loss. In severer cases the tongue papillae may be smoothed out and there may be signs of glossitis, moderate enlargement of the spleen and swelling around the malleoli caused either by hypoproteinaemia or impaired capillary permeability under the effect of anaemia (localized swelling).

The disease usually sets in unnoticeably, predominantly at the age of about 40. Both males and females suffer from it. Many of the clinical manifestations may be attributed to anaemia.

Abnormalities in the nervous system are revealed in approximately 80 per cent of the patients. They are manifested by paraesthesia, disturbed coordination in movements and deep and vibration sensitivity, and diminished, in some cases total absence, of tendon reflexes. In the mildest cases the patients complain of numbness and a sensation of prickling in the extremities. In severer cases the gait is abnormal, and the patient cannot button up his clothes, keep his balance in Romberg's position or perform other coordinated move-

ments. In the direst of cases there are loss of vision, absence of tendon reflexes, paraplegia, disturbed function of the urinary bladder and rectum. A change in personality sometimes occurs with hallucinations, lapses of memory, and disorientation. The neurological disorders in vitamin B_{12} deficiency are explained by affection of the peripheral nerves and the posterior and lateral columns of the spinal cord. Absence of free hydrochloric acid in the gastric juice or a sharp decrease in the rate of its secretion is found in almost every case of pernicious anaemia. Achlorhydria and low hour tension of gastric juice secretion are detected both during an exacerbation of the disease and after the onset of a remission. The inability to secrete free hydrochloric acid after a subcutaneous pentagastrin injection is one of the most important diagnostic signs of pernicious anaemia. The lack of free hydrochloric acid provides favourable conditions for dissemination of bacteria in the small intestine. A considerable number of cases with achylia-induced diarrhoea in pernicious anaemia is caused by concomitant dysbacteriosis which may noticeably increase vitamin B_{12} deficiency in the body of the patient.

Bone marrow puncture during a recurrence of the disease demonstrates a megaloblastic type of erythropoiesis. A great number of promegaloblasts and basophilic and polychromatophilic megaloblasts are always found in the smear. The last named persist after anaemia disappears (according to the peripheral blood values). The bone marrow smear always contains more or less cells in a state of mitosis. Megaloblastic bone marrow changes to normoblastic approximately one or two days after injection of a few milligrams of vitamin B_{12}. Giant metamyelocytes and polysegmented neutrophils are the second characteristic sign of vitamin B_{12} or folic acid deficiency in the body. This sign is more stable and persists for some time even after specific therapy is begun.

Macrocytosis and hyperchromia are detected in peripheral blood in every case of non-complicated and untreated pernicious anaemia. The mean red-cell volume almost always exceeds 100 μm^3. The mean haemoglobin concentration in the cell usually increases and is more than 30-35 per cent. A peripheral blood smear always demonstrates anisocytosis, poikilocytosis and oval macrocytes and, in severer cases, normoblasts. The presence of hypersegmented granulocytes in the blood smear is also considered a characteristic sign of vitamin B_{12} and folic acid deficiency. The content of vitamin B_{12} in blood of patients with untreated pernicious anaemia is drastically reduced and rarely reaches 200 pg/ml, and in some cases is even below 100 pg/ml. The content of indirect bilirubin in the blood is moderately increased.

On summing up we can state that the principal diagnostic signs of anaemia caused by vitamin B_{12} deficiency are as follows: macrocytosis and hyperchromia of the red cells, megaloblastic type

of erythropoiesis, pentagastrin-resistant achlorhydria, and signs of affection of the posterior and lateral columns of the spinal cord. The diagnosis is confirmed by the ability of vitamin B_{12} to induce a reticulocytic crisis and change the megaloblastic type of erythropoiesis to the normoblastic type. Antibodies to the intrinsic factor are found often but not in every case of the disease.

In some children pernicious anaemia does not differ from the disease in adults, in others it develops as the result of selected inability of the gastric mucosa to secrete the intrinsic factor. The mucous membrane of the stomach in these patients has a normal histological structure and is capable of secreting free hydrochloric acid. No antibodies to the intrinsic factor were found in these patients (McIntyre et al., 1965). A remission occurs after the prescription of parenteral vitamin B_{12}. The disease recurs if treatment is discontinued.

Vitamin B_{12} deficiency is sometimes encountered in children whose gastric mucosa is capable of secreting both hydrochloric acid and the intrinsic factor. It does not differ histologically from the normal mucous membrane. The intrinsic factor of these patients does not differ immunologically from the intrinsic factor of healthy individuals but it is deficient functionally because it has no effect on vitamin B_{12} absorption in the small intestine (Katz et al., 1972). Proteinuria is found in all patients. Malabsorption of vitamin B_{12} in such cases is attributed to anomalous structure of the iliac mucosa (MacKenzie et al., 1972). The described type of vitamin B_{12} malabsorption is designated the Groesbeck-Imerslund syndrome.

The clinical picture of pernicious anaemia may also be encountered in patients with a normal content of vitamin B_{12} in blood serum. Gimpert et al. (1975) observed it in members of one family. The development of vitamin B_{12} deficiency in such cases is attributed to deficiency of transcobalamine II in the patient's blood.

Following gastrectomy, the body is completely deprived of mucosal cells producing the intrinsic factor. Patients who underwent gastrectomy, just as patients with pernicious anaemia, require regular prescription of vitamin B_{12}. If they do not receive it they develop signs of vitamin B_{12} deficiency five to seven years after the operation. After partial resection of the stomach these signs appear much later and only in some of the patients. Half-period excretion of vitamin B_{12} is one year on the average. This is precisely the explanation for the very late development of the signs of its deficiency in patients who had been operated on.

The afferent loop syndrome develops in some patients subjected to Billroth II operation or its modifications. Stasis of the intestinal contents and decreased acidity of the gastric juice are conducive to the intensified growth of bacteria in the afferent loop. Dissemination of the bacteria in the small intestine is sometimes so severe that

the bacteria inhabiting it become antagonistic rivals of the intrinsic factor for winning vitamin B_{12}. Recovery is achieved by suppressing the intestinal flora with antibiotics. The stated above is also true of the bacterial flora developing in the ileum with diverticulitis. The broad tapeworm is also capable of assimilating vitamin B_{12}, thus causing the characteristic clinical picture of its deficiency in the body. After vermifuge treatment the patient fully recovers with no additional therapy.

Vitamin B_{12} deficiency is sometimes encountered in diseases of the distal ileal segment which are listed in Supplement II-3. The reserves of vitamin B_{12} in the body are sufficiently great, whereas the requirements in it are negligible. That is why a diet with a mild content of animal protein is effective in preventing the development of hypovitaminosis.

Folic acid. The term 'folic acid' designates a group of substances one of which, pteroylglutamic acid, participates in intermediate metabolism of a human. Folic acid is present in almost all foods, and the liver and plant leaves are particularly rich in it. It is rapidly destroyed by heating and its content in the diet therefore to a considerable degree depends on the way the food is prepared. After it is released from its complex with the dietary proteins, folic acid is absorbed in the jejunum.

The body reserves of folic acid are negligible, so that the clinical signs of macrocytic anaemia appear just a few weeks after folic acid had been removed from the diet, or three-to-four weeks after the beginning of marked disorders in its absorption.

Folic acid deficiency in the body is usually a consequence of its lack in the diet or its malabsorption in the proximal segments of the jejunum (Supplement II-4). Both of these factors act simultaneously in most cases.

It is our experience that folic acid deficiency is almost constantly encountered in coeliac disease, which is marked by affection mainly of the proximal segment of the jejunum. We always encountered folic acid deficiency in tumours of this segment (lymphosarcoma, lymphogranulomatosis) and in ulcer of the jejunum. Jejunotomy always results in the development of the clinical signs of folic acid deficiency just as resection of the ileum leads to vitamin B_{12} deficiency. Folic acid deficiency also occurs in diffuse affections of the intestine encountered in amyloidosis, Whippler's disease, and scleroderma. Dissemination of bacteria in the small intestine has no noticeable effect on folic acid absorption. It is disturbed under the effect of alcohol, antispastics, and contraceptives.

Megaloblastic anaemia often develops in children kept on milk with a deficient content of folic acid, the requirements in which are sharply increased during pregnancy. Folic acid deficiency in the body of a pregnant woman usually begins with the appearance of

hypersegmented neutrophils. The appearance in the peripheral blood of megaloblasts in severe haemolytic anaemia is explained by folic acid deficiency resulting from its increased consumption by the dividing bone marrow cells. Congenital defects in folic acid absorption have also been described, in which megaloblastic anaemia is usually attended with epilepsy, retarded mental development, and other signs of affection of the nervous system.

Anaemia in folic acid deficiency in the body is identical in haematological values with anaemia resulting from vitamin B_{12} deficiency. These two anaemias are distinguished one from the other by the attendant signs. Pentagastrin-resistant achlorhydria is encountered almost in every case with anaemia caused by vitamin B_{12} deficiency. In folic acid deficiency anaemia the secretion of free hydrochloric acid is maintained.

Severe diarrhoea and mild signs of affection of the nervous system are characteristic of anaemia induced by lack of folic acid. Anaemia caused by lack of vitamin B_{12} is usually attended with clear-cut symptoms of affection of the posterior and lateral columns of the spinal cord. Diarrhoea and other signs of the malabsorption syndrome are very moderate in such a case. The test for the blood vitamin B_{12} concentration and Schilling's test dissolve all doubt in diagnostically unclear cases.

The principle of Schilling's test consists in the following. The person examined is given radioactive vitamin B_{12} (usually 0.5 μ Ci of ^{57}Co-cyanocobalamine) orally. At the same time he is given an intramuscular injection of 1 mg of ordinary vitamin B_{12}. It can be accepted that vitamin B_{12} absorption is impaired if the amount of radioactive vitamin B_{12} in a 24-hour volume of urine of the person examined is less than 7 per cent of the amount taken orally. When the result is questionable the test is repeated, but this time 60 mg of the intrinsic factor derived from a hog's stomach is prescribed simultaneously with radioactive vitamin B_{12}. A normal content of vitamin B_{12} in the daily urine in the second test indicates that vitamin B_{12} absorption has improved because of the added intrinsic factor.

In conducting Schilling's test, one should bear in mind that its results depend on the severity of bacterial dissemination in the small intestine, which is often encountered in diverticulitis and the afferent loop syndrome. It is therefore recommended to perform Schilling's test in gastrectomized patients with signs of the malabsorption syndrome only after 10-12-day treatment with tetracycline or 6-8-day treatment with enterosediv or rifadin.

It is more difficult to make the diagnosis of pernicious anaemia in patients with signs of nervous system affection who had already been treated with vitamin B_{12} or folic acid and in whom the megaloblastic type of erythropoiesis had changed to the normoblastic

type. The test for free hydrochloric acid in the gastric secretion proves to be very valuable in such cases. The diagnosis of pernicious anaemia may be practically ruled out if free hydrochloric acid appears with the prescription of pentagastrin. If achlorhydria is preserved, Schilling's test is recommended; it assesses the ability of the iliac mucosa to absorb the labelled vitamin B_{12}.

Disorders of Iron Absorption and Metabolism

Iron absorption is determined by the interrelationship of three principal factors: the amount of iron in the lumen of the small intestine, the form of its cations, and the functional state of the mucous membrane. Contemporary man observing a mixed diet utilizes 10-20 mg of iron daily, mainly for the formation of myeglobin and haemoglobin. About 10 per cent of dietary iron is absorbed and an approximately equal amount is lost from the body.

The iron is released from its bond with the protein in the stomach. Under the effect of ascorbic acid contained in the diet, ferric iron changes to ferrous iron. In the acid gastric content, ferrous iron binds with mucopolysaccharide and forms a large iron complex. Small complexes form in the duodenum from the stable macrocomplex. They consist of iron, ascorbic and citric acids, hexoses and some amino acids, cystein in particular, and are mainly absorbed in the proximal part of the small intestine.

On entering the parts of the small intestine with pH higher than that in the stomach, iron is polymerized into a large colloid complex. The precipitated iron is excreted from the body as a hydroxide. Atrophy of the gastric mucosa reduces the capacity for splitting the dietary protein and is conducive to the development of iron deficiency in the body.

After haemoglobin and myoglobin splitting in the stomach haem is released. In the duodenum it is exposed to the effect of pancreatic enzymes which prevent its polymerization. In deficient pancreatic external secretion, absorption of haem by the duodenal mucosa is drastically disturbed because of its rapid polymerization to overlarge complexes. Iron reserves in the body in diseases of the duodenum are complemented by small amounts of haem which is absorbed in unchanged form.

A larger part of the absorbed iron rapidly enters the blood plasma where it binds with transferrin. A small part binds with apoferritin and remains in the cell in the form of a mycelle. This iron is lost together with the desquamated intestinal epithelial cells. After entering the cell, haem undergoes splitting and the iron released from it is assimilated. Iron is mainly absorbed in the duodenum and the initial segment of the jejunum. The mechanisms regulating iron

absorption are not ultimately clear, but it has been firmly established that it is intensified in iron deficiency and delayed in the increase of its reserves in the body.

Iron deficiency anaemia is the most common type of anaemia. Formerly it was mostly of alimentary origin. At present the dietary factor no longer plays the decisive role and anaemia usually develops under the effect of a complex of causes, principally of increased body requirements in iron, blood loss, and iron malabsorption.

The requirements of the body in iron increase sharply during pregnancy and in the period of intense growth. Girls have anaemia in the period of maturation more frequently than boys because of the unfavourable combination of increased iron requirements due to rapid growth and the beginning of blood losses which sometimes (e.g. in microcystic degeneration of ovaries and in dysovarian haemorrhages) may be considerable.

Blood losses are considered to be the most frequent cause of iron deficiency anaemia. In most cases they occur from defects in the mucous membrane of the gastro-intestinal tract. Anaemias caused by repeated nasal or haemorrhoidal bleedings are particularly common. Sometimes iron deficiency anaemia is caused by thrombocytopenic purpura, haemophilia, telangiectasia, diaphragmatic hernia, erosion, ulcer and tumour of the gastro-intestinal tract, and uterine haemorrhages.

Iron deficiency anaemia may be linked with haemolysis which is among the frequent complications in patients with valve prostheses.

Iron malabsorption is often encountered in patients after gastric resection, in enterocolitis, coeliac disease and duodenitis.

Almost all patients with iron deficiency anaemia who apply for medical aid complain of weakness, dyspnoea even in mild physical exertion, dizziness, and dimness, which are usually attended with throbbing pain in the head. A much rarer occurrence is sideropenic (postcricoid) dysphagia combined with glossitis (Plummer-Vinson's syndrome). These complaints are made most constantly after large blood losses and by patients with diarrhoea and post-resection syndromes.

Clinical examination reveals pallor of the skin and paleness of the mucous membranes, cracking at the corners of the mouth, atrophy of the tongue papillae, and sometimes glossitis and spoon-shaped abnormally fragile nails. The spleen is sometimes slightly enlarged and its painless border protrudes by 1-2 cm from under the left costal margin. The pronounced character of cardiovascular disorders depends on the severity of anaemia. Vascular murmurs (e.g. humming-top murmur) and a systolic murmur are encountered in milder cases. With a drop in the blood haemoglobin content below 50 g/l, the heart dilates. Achlorhydria is observed in approximately half the patients; it does not disappear after anaemia is corrected.

Iron deficiency in the body may exist with no changes in red cell morphology. With gradual progress of the deficiency, first hypochromia and later microcytosis develop. In severe iron deficiency anaemia, the mean volume of the red cell is less than 80 μm^3, the haemoglobin content in it falls below 30 pg, the concentration of haemoglobin below 30 per cent. Poikilocytosis and anisocytosis appear. Normoblasts are found in the peripheral blood in severe anaemia. The blood platelet count in iron deficiency anaemia is drastically increased in some cases and reduced in others. Blood bilirubin is sometimes slightly elevated.

The blood iron content is below normal value (500-1000 µg/l) and usually less than 400 µg/l. Low values of transferrin saturation are of no diagnostic significance, because they are encountered not only in iron deficiency anaemia but in many infections. Sternal puncture reveals a normoblastic type of haemopoiesis. The erythroblast count may be as high as 30 per cent. A drastic decrease or almost complete disappearance of haemosiderin granules is a characteristic feature of these cells. The siderocyte content in peripheral blood is also reduced. Iron deficiency anaemia may be encountered together with other anaemias (e.g. pernicious anaemia).

Approximately 90 per cent of all microcytic and hypochromic anaemias are caused by lack of iron in the organism. The diagnosis of this type of anaemia must always be verified by a test for iron concentration in the blood. In order to decide upon the volume of therapeutic measures, it is necessary to identify the cause of anaemia. This task proves to be very difficult in some cases and many methods of examination have to be applied. The role of blood loss from the gastro-intestinal tract is determined by testing radioactivity in the faeces after intravenous injection of chromium-labelled red cells. This is followed by determining the absorptive ability of the small intestine and the possible connection of anaemia with red-cell haemolysis. The performance of this complex of measures noticeably reduces the number of the diagnosed 'idiopathic iron-deficiency anaemias'.

Hypochromic microcytic anaemia developing in deficiency of iron in the body resembles thalassaemia only remotely. The latter is also marked by hypochromaemia and a reduced red-cell volume. The differential diagnosis between these diseases is not difficult, as a rule. Thalassaemia is a congenital disease. Anaemia develops in the first year of the infant's life. Milder forms of thalassaemia must be distinguished more frequently from other haemoglobinopathies than from iron deficiency anaemia. A test for the concentration of iron in blood enables iron deficiency anaemia to be differentiated with assurance from thalassaemia in doubtful cases. The blood iron content is always reduced in the former but always increased in the latter. A constantly high reticulocytosis, enlarged liver and

spleen help distinguish thalassaemia from iron deficiency anaemia.

Sideroblastic anaemia frequently proves to be hypochromic and microcytic. Poikilocytosis, anisocytosis and a normal or increased number of sideroblasts are found in the peripheral blood of these patients. The reticulocyte count is either normal or reduced. Signs of normoblastic erythropoiesis are detected in a bone-marrow aspirate. The number of sideroblasts is always considerably increased. Megaloblastic hyperplasia of the bone marrow is revealed in some patients. Macrocytes predominate in the peripheral blood of these patients. The blood serum iron content is increased, often above 200 μg/l.

Sideroblastic anaemia, like iron deficiency anaemia, is encountered at any age. Most patients are well nourished and lack the common clinical symptoms of pyridoxine deficiency. Enlargement of the liver and spleen is revealed in half of the cases. The prescription of large pyridoxine doses is attended with the development of reticulocytic crisis in four to ten days from the beginning of treatment in these patients. The reticulocyte count is sometimes as high as 50 per cent. The iron content in the blood reduces to a normal level at the same time. Treatment with iron preparations is ineffective. Iron deficiency anaemia is distinguished from pyridoxine-sensitive anaemia by a low content of iron in blood serum and a reduced content of sideroblasts in blood and bone marrow. These two types of anaemia can be distinguished by trial prescription of pyridoxine. Iron preparations are contraindicated in sideroblastic anaemias.

Sideroblastic anaemias are sometimes among the manifestations of the toxic effect of lead and anti-tuberculous agents (isoniazid, cycloserine, pyrazinamide) on erythropoiesis. It is known that lead inhibits haem synthesis in the cells without blocking it completely. The prescription of pyridoxine causes marked diminution of the signs of anaemia and peripheral neuritis in patients with drug sideroblastic anaemia, but recovery occurs only after the agents mentioned above are discontinued. These agents possibly either cause pyridoxine insufficiency or hinder its assimilation by the cells.

Sideroblastic anaemia or the appearance in the blood of sideroblasts without the development of anaemia is sometimes encountered in multiple myeloma, uraemia, lymphogranulomatosis, diseases of the liver, leucoses, diffuse connective-tissue diseases, metastasis of carcinoma to the bone marrow, and in some other diseases. Successful treatment of the principal disease leads to the disappearance of sideroblasts. Such a result sometimes occurs after the prescription of pyridoxine or folic acid. Secondary sideroblastic anaemia is usually benign and only in rare cases complicated by hepatosplenomegaly and haemochromatosis. Regular and comprehensive examination of patients suffering from sideroblastic anaemia showed that leukaemia develops in many of them over a longer or shorter

period of time (Kushner et al., 1971; Leavell and Thorup, 1976).

Aplastic and Hypoplastic Anaemia

The terms 'aplastic' and 'hypoplastic' anaemia are used to designate a group of diseases and syndromes the underlying factor of which in most cases is either isolated hypoplasia of the erythrocytic stem or hypoplasia of several bone marrow germs. Both forms of anaemia may be congenital or acquired. Pseudoplastic anaemias whose development is associated with deep disturbances in the structure and function of erythroblasts and red cells are commonly included in this group. A large number of erythroblasts are found in the bone marrow of these patients, despite the marked anaemia.

From the contemporary standpoint, hypoplastic anaemia is a disease of the bone marrow manifested by its inability to produce red cells. In most cases damage to the leucocytic and megakaryocytic germs is found, which is manifested by neutropenia and thrombocytopenia. Functional torpor of the bone marrow may occur at any age. In our times, hypoplastic anaemia is most often caused by drugs and chemicals used for household needs as well as in industry and farming. The association of hypoplastic anaemia with the use of antibiotics, sulphanilamides, hypoglycaemic agents and preparations of gold is particularly common. Functional depression of the bone marrow often develops after contact with solvents (e.g. petrol) and insecticides. The cause of hypoplastic anaemia remains unclear in many cases which are therefore classified 'idiopathic'.

Congenital forms of hypoplastic anaemia usually set in incidiously, whereas the acquired forms often occur as an acute disease with high fever and a haemorrhagic syndrome. These features of the clinical picture have in the past served as grounds for calling the disease 'septic angina' or 'haemorrhagic aleukia'. Attention is drawn to the drastic pallor of the skin and paleness of the mucous membranes and sclerae. The liver and spleen are not enlarged. The cervical and submandibular lymph nodes are sometimes slightly enlarged in cases complicated by angina.

The clinical manifestations of the disease are to a great measure determined by the character of the bone marrow affection. In isolated lesion of the erythrocytic germ, the disease begins as severe 'refractory' anaemia. Simultaneous involvement of all germs produces a picture of panmyelophthisis. A disease beginning with affection of the megakaryocytic germ is usually mistaken for thrombocytopenic purpura for some time. An earlier or predominant affection of the myeloid germ is manifested at the beginning as agranulocytosis or agranulocytic angina. The mentioned initial manifestations

are replaced after some time by a developed picture of the disease with simultaneous affection of all three germs of the bone marrow. On recovery thrombocytopenia disappears last of all (Bottiger and Westerhelm, 1972).

Peripheral blood test usually reveals pancytopenia (80 per cent of cases), anaemia (8-10 per cent), anaemia and neutropenia (7-8 per cent) and anaemia and thrombocytopenia (3-5 per cent). The blood lymphocyte count may be increased, normal or reduced. The results of sternal puncture and trepanobiopsy showed a reduced number of cells in the bone marrow in 74 per cent of cases. In the remaining cases the cell content was normal or increased. Aplasia or hypoplasia of all three bone-marrow germs was found in 74 per cent, of two germs in 5 per cent and of one germ in 12 per cent of cases. An increased number of lymphocytes and plasma cells was often revealed in the bone marrow.

Partial hypoplasia of the erythrocytic germ is manifested by normocytic or mild macrocytic anaemia. The number of leucocytes and blood platelets at the onset of the disease remains normal. Thrombocytopenia or pancytopenia with the haemorrhagic and infectious complications characteristic of them develops later. About half the patients are found to have thymoma, the surgical removal of which often leads to remissions (Krantz, 1973; Marmont et al., 1975). Hypoplastic anaemia with isolated inhibition of erythropoiesis may be the first clinical manifestation of a carcinoma. This type of anaemia is also encountered as a congenital disease (erythrogenesis imperfecta) in the newborns or children of the first year of life.

Familial hypoplastic pancytopenia is encountered in two types: without or with congenital anomalies. The latter form was studied by Fanconi who suggests the following diagnostic criteria on the basis of long-term follow-up of 129 patients: progressive pancytopenia, hyperpigmentation of the skin, marked retardation of growth, hypogonadism and skeletal anomalies. Strabismus (22 per cent), microcephalus (40 per cent) and retarded mental development (17 per cent) are also often encountered. Anaemia usually develops on the seventh or eighth year of life. The bone marrow may be active at the beginning of the disease, but is replaced by fatty tissue in the late stages.

The peripheral blood picture characteristic of aplastic anaemia is sometimes encountered in patients with markedly intensified erythropoiesis in the bone marrow. Some authors designate this syndrome *pseudoplastic anaemia*, others call it *ineffective erythropoiesis*. In addition to hyperplasia of the bone marrow erythrocytic germ and pancytopenia in peripheral blood, a characteristic sign of this syndrome is a noticeable increase in haemolysis which is manifested by reticulocytosis and increased concentration of non-conjugat-

ed bilirubin in the blood. One part of the deficient cells of the erythrocytic series is haemolysed in the bone marrow, the other is doomed to premature destruction in the spleen and other organs.

Ineffectvie erythropoiesis is sometimes encountered in anaemias caused by vitamin B_{12} and folic acid deficiency, leukaemia, erythroleukaemia, myeloproliferative syndromes, thalassaemia, sideroblastic anaemia and in congenital dyserythropoiesis. The most characteristic symptom of this last disease is non-simultaneous maturation of the nucleus and protoplasm of the cells of the erythrocytic series. The cell protoplasm is basophilic and contains a great number of vacuoles. One cell may contain several nuclei which are sometimes connected with one another by chromatin bridges ('giant blasts'). Cells with pyknotic nuclei are found next to the typical megaloblasts. Maldonado and Taswell (1974) report that the disease is sometimes manifested only at elderly and old age.

Aplastic and hypoplastic anaemia is among the diseases which are recognized with great difficulty. Their differentiation from leukaemia is particularly difficult. Both diseases may occur suddenly. Fever and anaemia predominate in the clinical picture in one case and fever and the haemorrhagic syndrome in another. An even greater similarity is seen in these diseases when they set insidiously. They are both displayed as progressive anaemia which is sometimes combined with neutropenia and thrombocytopenia. The differential diagnosis is particularly difficult in children because of the instability of their blood composition.

Although acute leucosis resembles aplastic anaemia it nevertheless differs in many cases in the severity of some of the signs. As it is noted above, the liver and spleen are not enlarged in aplastic anaemia but are often mildly enlarged in acute leucosis. The lymph nodes are not enlarged in aplastic anaemia, but moderate enlargement of the cervical nodes is sometimes found in acute leucosis. The diagnostic significance of these signs grows in cases with no tonsillitis or necrosis in the oral cavity. Spontaneous pain in the sternum or its tenderness to palpation is often noted in acute leucosis; it does not occur in patients with aplastic anaemia. We do not insist that this sign is of diagnostic importance because we had only a few patients with aplastic anaemia. Bilateral enlargement of the submaxillary salivary glands is occasionally encountered in acute leucosis but has not been described in aplastic anaemia.

Study of bone-marrow haemopoiesis reveals information, as a rule, that makes the differentiation of these two diseases much easier. In aplastic anaemia the active bone marrow is replaced almost completely by yellow marrow. The bone-marrow stroma is sharply oedematous. Trepanobiopsy reveals occasional foci of hyperplasia with a large number of immature cell elements of leucopoiesis and erythropoiesis in the fatty tissue. In less severe cases the oedema

of the stroma is mild and though the number of fat cells is increased, bone-marrow haematopoiesis is nonetheless preserved. A considerable number of plasma cells are contained in the bone marrow besides the cells of the erythrocytic series.

The method of sternal puncture suggested by Arinkin in 1929 does not yield sufficiently reliable grounds in some cases for making the differential diagnosis between aplastic anaemia and leukaemia. The bone marrow cannot be collected when the needle enters the foci of fatty infiltration, and the aspirated material may consist mainly of non-differentiated cells of the myeloid series when the needle enters the focus of hyperplasia (Fainshtein, 1965). The common diagnostic rule stating that the more blast cells there are in the aspirate, the more probable the diagnosis of leucosis, does not apply to such cases.

The blood picture in aplastic anaemia may be no different from that in acute leucosis from the very onset to the end of the disease. Sometimes it demonstrates only the onset of leucosis whose other clinical signs may appear several months or several years after the beginning of the disease. In some cases the final diagnosis may be made only after quite a long period of surveillance of the course of the disease and the character of changes in the blood and bone marrow.

Chronic myeloleucosis at times makes its appearance as aplastic or hypoplastic anaemia which precedes its other signs by several years. The blood myeloblast count in such cases may be negligible and sometimes these cells may be detected only in blood smears prepared from a centrifuged blood leucocytic fraction. It is recommended to perform this examination before sternal puncture. It is valuable not only in detecting leukaemias, but also in differentiating one type from another. The diagnostic difficulty usually disappears with the appearance of enlarged lymph nodes, hepato- and splenomegaly. By this time the leucocyte count considerably increases and juvenile forms which are very important for the diagnosis (promyeloblasts, myeloblasts, myelocytes) are already detected in peripheral blood.

Malignant tumours with metastatic spread to the bone marrow are often complicated by anaemias which take a progressive course. Such anaemias are usually normocytic and hyperchromic. Sometimes X-ray examination cannot demonstrate signs of bone involvement, in which case severe anaemia with the presence of normoblasts in the blood proves to be the only manifestation of metastatic bone-marrow affection. Some time later the immature cells of the erythrocytic and myeloid series may disappear from the peripheral blood but may reappear in it after a certain interval of time. A normal blood picture does not rule out carcinoma of the bones. Anaemia with normoblasts, juvenile neutrophils, and myelocytes in blood

of elderly and old patients is usually caused by metastasis of carcinoma to the bone marrow. Further diagnostic examination of the patients should be aimed at finding the primary tumour.

Severe anaemia with marked pancytopenia is sometimes encountered in untreated pernicious anaemia. Its differential diagnosis with aplastic anaemia is rarely difficult. These two diseases differ one from the other in the appearance of the skin, sclerae and mucous membranes, which have a yellowish tinge in patients with pernicious anaemia and are pale white in those with aplastic and hypoplastic anaemia. Glossitis, splenomegaly and signs of nervous system affection are characteristic of pernicious anaemia but are not encountered in aplastic anaemia. In doubtful cases the final diagnosis is based on the results of sternal puncture and trial vitamin B_{12} therapy.

Haemolytic Anaemia

The life and functional activity of a normal red cell last approximately 120 days. After disintegration of the cell the haem of its haemoglobin is engulfed by the reticuloendothelial cells which convert it to non-conjugated bilirubin. On entering the liver this bilirubin binds with glucuronic acid and is then secreted into the gastrointestinal tract from which it is excreted as stercobilin. In haemolytic anaemia the life span of a red cell is shorter. As a result, the erythrocytic bone-marrow germ is hyperplastic and the reticulocyte count in peripheral blood is increased. Accelerated red-cell disintegration is attended with splenomegaly.

Haemolytic anaemias are commonly divided into congenital, caused by deficient red-cell structure and function, and acquired in which red-cell destruction occurs under the effect of environmental factors.

Congenital Haemolytic Anaemia

Anomaly of red-cell membrane. The clinical picture of *congenital spherocytosis*, the prevalent type of haemolytic anaemia in Europe, was described in detail for the first time in 1900 by Minkowski under the name 'congenital haemolytic jaundice'. In 1907 Chauffard pointed out two new signs of the disease, namely, high reticulocytosis and reduced osmotic resistance of the red cells. The disease develops in the first half of life and sometimes soon after birth. It may be asymptomatic and the sick individual leads an active life because anaemia is either hardly manifested or absent. A permanently high reticulocytosis and hyperplasia of the bone-marrow erythroid germ are the only signs of the disease in such cases.

In most instances congenital spherocytosis follows a chronic course with exacerbations from time to time called aplastic crises. An exacerbation occurs suddenly with fever attended with nausea, vomiting and abdominal pain. Severe crises are complicated by collapse. Anaemia, leucopenia and thrombocytopenia develop rapidly during the crisis. The reticulocyte count and bilirubin content in the blood drop sharply. The bone marrow becomes aplastic. Milder exacerbations of the disease are attended with intensified jaundice and fever. These exacerbations are usually associated with hepatic colic or some infectious disease.

Exacerbation of calculous cholecystitis, which is revealed in almost every case of spherocytosis, is sometimes complicated by obstructive jaundice. Moderate hepatomegaly is found almost in every case and splenomegaly in each case of congenital spherocytosis. When there are no aplastic crises and hepatic colic, the patient feels quite well in confirmation of the saying that 'he is more jaundiced than ill'.

The average red-cell volume in congenital spherocytosis is normal or slightly reduced. The average haemoglobin content in the cell is always increased. The reticulocyte count ranges from 5 to 20 per cent.

The diagnosis of congenital spherocytosis is easily made in most cases. The combination of moderate anaemia, splenomegaly and mild jaundice is a characteristic sign. Stable reticulocytosis, reduced red-cell osmotic resistance, familial character of the disease, and the favourable effect of splenectomy confirm the diagnosis.

Congenital elliptocytosis is a rare disease. It usually occurs as an asymptomatic anomaly, but approximately 12 per cent of patients show signs of increased haemolysis and mild anaemia. About 25 to 90 per cent of the red cells possess the characteristic form of ellipses. Poikilocytes, microcytes and other anomalous red-cell forms appear only in association with crises. Splenomegaly is encountered only in patients with anaemia. After splenectomy anaemia disappears, but the altered shape of the red cells remains and proves to be the only sign of the disease.

Congenital stomatocytosis is a syndrome in which the red cells are shaped like a vase in the blood, while in a dry smear a slit-like opening remotely resembling a mouth is seen in their centre. The disease is asymptomatic or mild haemolytic anaemia is present. Transient stomatocytosis with haemolytic anaemia sometimes develops after alcohol intake.

Intracellular enzyme deficiency. Haemolytic anaemia caused by a *deficient content of glucose-6-phosphate dehydrogenase* (G6PD) was prevalent among American soldiers given antimalarial drugs for a long time for preventive purposes. Detailed study of the disease undertaken after 1950 revealed that G6PD deficiency is trans-

mitted through sex chromosomes and that the disease is prevalent all over the world. In the Soviet Union this anomaly is mostly encountered among the populations of Azerbaijan.

G6PD deficiency is displayed in two forms. The carriers of this anomaly, most of whom live in northern Europe, suffer from mild haemolytic anaemia all their life, which exacerbates in bacterial and virus infections and in medication with drugs listed in Supplement II-5 (Luzzatto, 1975). Before its true cause was established, the disease was classified as non-spherocytic haemolytic anaemia. The carriers of this anomaly living in the coastal areas of the Mediterranean acquire haemolytic anaemia only after taking these drugs.

Acute haemolysis becomes evident on the second to fourth day of medication and is almost always attended with hyperbilirubinaemia and haemoglobinuria. The blood reticulocyte count increases gradually and reaches maximum on the 10th to 12th day of the disease. Mature red cells undergo haemolysis, the reticulocytes are not destroyed. Haemolytic crisis may be induced by infection, both bacterial and viral, and is also encountered in diabetic coma.

About 80 varieties of G6PD anomalies have been described to date. Approximately half of the carriers of these varieties have no clinical manifestations of the disease (Yoshida, 1973).

Deficiency of enzymes of the pentoso-phosphate cycle and glutathione system (glutathione-reductase, glutathione-synthetase, glutathione-peroxidase, gamma-glutamil-cysteine-synthetase) is inherited as an autosomal recessive trait. The carriers of these anomalies are quite common in Germany. They all suffer from chronic haemolytic anaemia which exacerbates noticeably after medication with drugs listed in Supplement II-5 and during infectious diseases.

Congenital non-spherocytic haemolytic anaemia caused by deficiency of enzymes contributing to anaerobic glycolysis began to be studied in detail in 1961. *Pyruvate kinase deficiency* proved to be the most common cause of this type of haemolytic anaemia. The anomaly is inherited as an autosomal recessive trait. The sick individuals differ sharply in the severity of the disease. Splenectomy leads to noticeable abatement of anaemia but not to complete cessation of haemolysis. Haemolytic anaemia resulting from deficiency of other glycolytic enzymes is very rare.

Congenital non-spherocytic haemolytic anaemias caused by G6PD deficiency are distinguished from anaemias induced by pyruvate kinase deficiency by means of the autohaemolysis test. Autohaemolysis of red cells with G6PD deficiency is either normal or slightly intensified. In the last case it reduces markedly after the addition of glucose. Autohaemolysis of red cells with pyruvate kinase deficiency is always intensified. After the addition of glucose it does not decrease.

Haemoglobinopathies. *Sickle-cell anaemia.* More than 100 haemo-

globin anomalies have been described to date among which HbS is of the highest clinical significance. The structural peculiarities of haemoglobin are inherited. A child suffers from sickle-cell anaemia if the HbS gene is transmitted to it by both parents. When the child receives this gene from one parent, it is found to have only the sickle-cell anomaly. Both the disease and the anomaly are mainly spread among people of Negro origin.

Sickle-cell anaemia is a chronic disease which exacerbates now and again (crises). Three types of crises are distinguished, among which the aplastic crisis is the severest. All its clinical manifestations are similar to those of aplastic crises in other haemolytic anaemias. A pain crisis begins with the appearance of aching pain in the knees or lower limbs on waking up. The pain gradually intensifies and sometimes spreads to the abdomen, back, upper limbs, neck, and head. The entire body may be racked with pain within several minutes or a few hours which continues for two or three hours or one or two days. Intolerable pains are sometimes suffered only in one half of the body or only in the limbs. Occurring suddenly and ceasing just as sharply, such pains (which even morphine fails to relieve in some cases) may appear regularly at intervals of a few weeks or once a year or once in several years.

Pains occurring as a result of anoxia or infarction of various organs are also referred to as crises. Infarctions develop particularly often in the spleen, kidneys, bones and lungs.

Non-healing ulcers usually on one, less frequently on both shins, are among the typical manifestations of the disease. Aggregation of sickled red blood cells occurs regularly in the capillaries of various organs and causes various disorders of their structure and function. Second infarctions of the lungs are usually attended only with pneumonia, but they sometimes cause the development of cor pulmonale. Infarction of the kidneys is manifested by haematuria. Sometimes it causes chronic renal insufficiency. Aseptic bone necroses result in severe skeletal deformities. The clinical picture of cerebral infarctions is determined by their size and localization.

The severity of anaemia depends on the course of the disease. During exacerbation anaemia intensifies noticeably. The reticulocyte content is also increased and often exceeds 20 per cent. During aplastic crises reticulocytosis disappears. The leucocyte count is increased to $10\text{-}15 \cdot 10^3$ per 1 μl.

The diagnosis of the disease is usually established from the combination of anaemia with splenomegaly, from a positive test for sickled red blood cells, and from detection of abnormal HbS. Sickle-cell anaemia is severe, as a rule. Most patients die in childhood, only a few live to the age of thirty. The congenital character of the disease makes its diagnostics much easier. The differential diagnosis is difficult only when there is acute abdominal pain which may

result both from acute purulent and other abdominal diseases inherent in all people and from transient anoxia or infarctions of the abdominal organs developing often in a sickle-cell anaemia crisis. The final diagnosis in such cases is guided by the results of a dynamic follow-up of the disease.

Thalassaemia. The features of the structure of skeletons discovered in archaeological excavations provide evidence that thalassaemia (a congenital disease caused by defective haemoglobin synthesis) was encountered in Southern Italy and Greece about 50 000 years ago. The disease is inherited and occurs in the homozygote (thalassaemia major) and heterozygote (thalassaemia minor) forms. In the Soviet Union this disease is encountered in Azerbaijan and Central Asia.

Thalassaemia minor is asymptomatic in most cases or is attended with mild haemolysis. The asymptomatic forms of the disease are detected only by laboratory examination of members of families suffering from thalassaemia major. Target-like red blood cells may be the only sign of thalassaemia minor. A great amount of abnormal haemoglobin A_2 is found in the blood of these patients. Symptomatic forms of thalassaemia minor are marked by moderate microcytic and hypochromic anaemia. The spleen is slightly enlarged, increased reticulocytosis and mild jaundice appear only at times. Red-cell osmotic resistance is increased.

Thalassaemia major sets in in childhood, usually during the first ten years of life. The children are pale and they tire easily. On examination attention is drawn to the abnormally large head, sharply high cheekbones, a caved-in nose and a dirty-yellowish skin. There are hepatomegaly and splenomegaly. Because of the enlarged spleen the abdomen is often markedly protruded. Chronic ulcers on the skin occur in many patients. The heart is markedly dilated and an apical systolic murmur is heard. Oedema of the subcutaneous tissue and hydrops of the cavities are often encountered. The earlier the disease begins, the more severe is its course. Most children with thalassaemia die before puberty from intercurrent infections or as a consequence of frequent blood transfusions.

Anaemia in thalassaemia is always microcytic and hypochromic. The average red-cell volume is often less than 60-70 μm^3. Examination of blood smears reveals poikilocytosis, anisocytosis and polychromatophilia and always a great number of normoblasts. The leucocyte count in blood is increased to $10\text{-}25 \cdot 10^3$ per 1 μl. From 50 to 90 per cent of blood haemoglobin is represented by its foetal variant.

The diagnosis of thalassaemia major is made rather easily. It is far more difficult to distinguish mild forms of thalassaemia from other types of haemolytic anaemia and from other haemoglobinopathies. In some cases thalassaemia has to be differentiated from

iron-deficiency anaemia. A tentative diagnosis of thalassaemia is made in combination of the following signs: the very young or young age of the patient, considerable enlargement of the liver and spleen, the discovery in peripheral blood of microcytosis, hypochromia, target cells and normoblasts. The diagnosis is verified by the results of electrophoretic examination of haemoglobin.

Other congenital haemoglobinopathies are less common than those mentioned above. Many 'unstable haemoglobins' have recently been described, whose carriers also suffer from haemolytic anaemia. Haemolysis in patients with unstable haemoglobins is mild, as a rule. Just as in patients with G6PD deficiency, typical haemolytic crises develop in patients with unstable haemoglobins only after the intake of drugs and poisons listed in Supplement II-5. The condition of these patients improves noticeably after removal of the spleen. Electrophoresis demonstrates many, but not all, unstable haemoglobins.

Acquired Haemolytic Anaemia

Auto-immune haemolytic anaemia. Two processes underlie all auto-allergic reactions: production of antibodies and proliferation of specifically sensitized effector cells which are, if not exclusively, mainly T-lymphocytes. The antigen determinants bind with specific receptors of immunocompetent cells. Some authors claim that one cell has receptors of only one type.

Under the effect of the antigen-receptor reaction, the cell begins producing antibodies which are the exact copy of the receptor present on its membrane. The antigen-antibody complex is firmly bound with the red-cell membrane in some cases and is easily detached from it in others. These circumstances are among the factors determining some of the peculiarities of the clinical manifestations of some types of acquired haemolytic anaemia.

Hayem, who revealed the main signs of this type of haemolytic anaemia, offered its first description: shortened life span of the red cells, hyperbilirubinaemia, increased stercobilin content in the faeces, reticulocytosis, and splenomegaly.

Auto-immune haemolytic anaemia is usually a complication of another disease, in which case it is called secondary, or symptomatic. When no concomitant disease is revealed, the anaemia is designated primary or idiopathic auto-immune haemolytic anaemia. It is distinguished from other types of acquired haemolytic anaemias by Coombs' antiglobulin test.

The mechanism of haemolysis is determined by the type of antibodies attaching to the surface of the red blood cell. Haemolysins are antibodies of the class M immunoglobulins bound with the com-

plement and fixated on the red cells. If the content of the complement is sufficient, these antibodies cause haemolysis of the red blood cell in an isotonic sodium chloride solution or within the vessels (intravascular haemolysis). Agglutinins are antibodies which cause only agglutination of the red blood cells. They are distinguished from haemolysins by a lesser complement content. Red corpuscles agglutinated by the class M immunoglobulin antibodies are removed from the blood stream mainly by the liver and partly by the spleen.

Antibodies belonging to class G immunoglobulins are called incomplete because of their small size. They usually do not fixate complement. Attaching themselves to the surface of the red blood cell, they cannot cause either its agglutination or haemolysis in isotonic sodium chloride solution or in blood. The antiglobulin test suggested by Coombs demonstrates this type of antibody to the red blood cells. Red corpuscles with class G immunoglobulin antibodies fixated on their surface are removed from circulation mostly by the spleen (Gell et al., 1976). Coombs' antiglobulin test yields a positive result in most cases of auto-immune haemolytic anaemia.

Auto-immune haemolytic anaemia with a positive Coombs' test is usually separated into anaemia with 'cold' and anaemia with 'warm' antibodies. Antibodies belonging to class M immunoglobulins are constantly detected in blood in pneumonia caused by *Mycoplasma pneumoniae*, lymphogranulomatosis, lymphosarcoma, systemic lupus erythematosus and cold paroxysmal haemoglobinuria. They are related to the group of cold antibodies. Class G immunoglobulin antibodies detected in idiopathic auto-immune haemolytic anaemia and in treatment with aldomet belong to the group of warm antibodies. They are encountered in approximately 70 per cent of patients suffering from auto-immune haemolytic anaemia.

The disease may begin gradually or set in suddenly. It is more common among females. The patients differ sharply in the degree of anaemia, fever, and weakness. Jaundice and haemoglobinuria occur in severe cases. When the disease is caused by cold antibodies, a picture of peripheral vasospasm often develops after chilling. The disease may last for many years, exacerbating now and then. In our experience the patients had hepatomegaly, splenomegaly, and stones in the gall bladder. Secondary auto-immune haemolytic anaemia at times precedes the principal disease by a few years. Its clinical picture is composed of signs of haemolytic anaemia and the principal disease.

In most cases auto-immune haemolytic anaemia is macrocytic because of the great number of reticulocytes. The number of leucocytes in blood is usually sharply increased. The content of other blood corpuscles may vary noticeably, both in different patients and

in one and the same patient. Erythrophagocytosis is considered a characteristic phenomenon. Coombs' direct test is positive in most patients with auto-immune haemolytic anaemia; in severer cases the indirect test is also positive. In some cases of the disease the test remains negative. Garraty and Petz (1975) explained this by the fact that the number of immunoglobulin G molecules on the red cells is far too small, whereas Chaplin (1973) claimed that this occurs because the antibodies causing haemolysis belong to class A immunoglobulins which, as is known, do not react with the standard Coombs' serum. Corticosteroid therapy is efficacious in both cases.

Paroxysmal cold haemoglobinuria. In 1904 Donath and Landsteiner established that the serum of patients with paroxysmal cold haemoglobinuria contains an antibody which is adsorbed on the surface of the red blood cell at a low temperature and which is capable of causing erythrocytolysis when the suspension of serum and red cells is heated to room or body temperature.

The Donath-Landsteiner antibodies are class G immunoglobulins and are active only in the presence of complement. Paroxysmal cold haemoglobinuria is classically linked with congenital syphilis and is a rare disease. A great number of cases with paroxysmal cold haemoglobinuria of non-syphilitic origin has now been described. It is sometimes encountered after measles, whooping cough, chickenpox and infectious mononucleosis.

The duration and severity of the disease differ in individual cases. Sometimes the patient has only one attack of haemoglobinuria, in other cases, the attacks recur in the duration of many years with the coming of the cold season. In typical cases the attack begins soon after chilling with general malaise which changes to a violent chill and a fever of 39-40°C. Excretion of dark red urine is noted immediately after the chill. Haemoglobinuria may continue several hours or several days. Mild jaundice and enlargement of the liver and spleen are found after the attack.

The Donath-Landsteiner antibodies are strictly specific and are auto-antibodies to a definite blood group (P). They are only detected soon after an attack and are not demonstrated between attacks. This distinguishes the cold paroxysmal haemoglobinuria syndrome from the cold haemagglutination syndrome in which antibodies to the red cells are also preserved between attacks.

Paroxysmal nocturnal haemoglobinuria (Marchiafava-Micheli syndrome) is a very rare disease. It is manifested by continuous intravascular haemolysis and haemoglobinuria which is most sharply pronounced on awakening. The chronic course of haemolysis is interrupted by exacerbations. Vascular thromboses often occur. The haemolysis is explained by hypersensitivity of the patient's red and white corpuscles and blood platelets to complement. Many

drugs, vaccines, and sera noticeably intensify haemolysis. They sometimes lead to the development of haemolytic crises. The attacks of haemoglobinuria are often associated with infectious diseases or occur during menstruation. Patients rarely survive over five years.

Haemosiderinuria is a permanent sign of the disease and should be disclosed in every case. Haemoglobinuria is an inconstant sign because in mild haemolysis the released haemoglobin is fully reabsorbed in the nephron tubules.

In many cases paroxysmal nocturnal haemoglobinuria begins as pancytopenia. Sirchia and Lewis (1975) report that in about 25 per cent of cases paroxysmal nocturnal haemoglobinuria is at first mistaken for aplastic anaemia. The correct diagnosis is established only when the patient's spleen becomes enlarged. The reaction to acidification of blood serum or the reaction intensifying complement activity may considerably help in the diagnosis of the disease.

Anaemias caused by mechanical destruction of red blood cells. Haemolytic anaemia sometimes results from mechanical destruction of the red blood cells. March haemoglobinuria sometimes developing in soldiers after long marches has been known from the end of the last century. The occurrence of this condition is now attributed to injury to the red cells in the foot capillaries as a result of the continuous impact of the sole foot against the hard shoe. March haemoglobinuria can be prevented by outfitting soldiers, runners, and hikers with elastic insoles.

Mechanical haemolysis is often encountered in patients with valve prostheses. The haemolysis in many cases is negligible, and the loss of red cells is easily compensated for by intensification of erythropoiesis. Anaemia develops only in severer cases. It is quite easy to make the diagnosis of traumatic haemolysis in patients with valve prostheses. The disease is manifested in increased concentration of haemoglobin in the plasma, haemosiderinuria, increased lactate dehydrogenase activity, appearance of schizocytes in a blood smear and reduced concentration of iron in the blood serum.

Angiopathic haemolytic anaemia results from damage to the red blood cells caused by the turbulent blood stream in the small vessels, stenosed segments of an artery, and in areas localized distally to the site of marked arterial stenosis. Such conditions may be encountered in severe arterial atherosclerosis, endarteritis obliterans, haemangioma, renal hypertension, arteritis nodosa and pulmonary hypertension. The cause of anaemia in these patients sometimes becomes obvious on examination of blood smears in which fragments of the red corpuscles are found. Microangiopathic haemolytic anaemia has been reproduced in experiments.

Acute haemolysis may occur when the body is exposed to the effect of physical and chemical factors. Haemolytic anaemia develops in

severe burns and in poisoning with chlorates, arsenics and copper.

Drug haemolytic anaemia does not occur very often. In some cases the drugs serve as a hapten which on binding with the plasma proteins becomes an antigen. The antigen-antibody complex binds with complement. When this complex dissociates, complement stays on the surface of the red cells. The activity of these immunocomplex mechanisms is responsible for haemolytic anaemia occurring sometimes in medication with quinidine, quinine, sulphanilamides, insulin, rifadin, PAS, isoniazid, tolbutamide, indomethacin, analgetics, and some other agents. This is a rare type of haemolytic anaemia. Haemolysis of the red cells takes place in the vessels and is attended with haemoglobinuria. Anaemia disappears soon after the drugs are discontinued.

In other cases, drugs (usually penicillin or ceporin) bind firmly with intact red blood cells. The antibodies react with penicillin, injure the red cells, and cause their haemolysis. This type of drug haemolytic anaemia is only encountered in treatment with very large doses of penicillin.

The possibility of haemolysis developing must be borne in mind in all cases of progressive anaemia in patients suffering from bacterial endocarditis or pulmonary abscess and treated with large doses of penicillin or ceporin. Haemolysis ceases immediately after the drug is discontinued. Coombs' reaction is positive for 60-80 days.

Some drugs, e.g. aldomet (methyldopa), methysergide, aminazine (chlorpromazine hydrochloride), diphenylhydantoin, induce the formation of antibodies against the red blood cells. Haemolytic anaemia in medication with these agents may be quite severe. Coombs' reaction stays positive for a long span of time after the drug is discontinued. The mechanism of the auto-immune process developing in treatment with these agents has not been ultimately disclosed. Haemolytic anaemia is encountered in approximately 1 per cent of patients treated for a long time with these agents.

Supplement II-1

Causes of Anaemia

I. Inhibition of erythropoiesis as a consequence of deficiency or disturbed metabolism of its dietetic factors.
   - Deficiency of protein in the diet or its increased loss through the gastrointestinal tract.
   - Deficiency of vitamin B_{12} and folic acid or their disturbed metabolism.
   - The Groesbeck-Imerslund syndrome.
   - Transcobalamine II deficiency.
   - Disorder of iron absorption and metabolism.

II. Functional bone-marrow deficiency (aplastic and hypoplastic anaemia).
   - Partial hypoplasia of the erythropoietic germ.
   - Total bone marrow hypoplasia.

Ineffective erythropoiesis (pseudoplastic anaemia).
Congenital dyserythropoiesis (incomplete erythropoiesis).
III. Blood loss.
Acute and chronic iron deficiency anaemia.
IV. Haemolysis (haemolytic anaemia).
1. Congenital haemolytic anaemia.
Anomaly of the erythrocytic membrane.
Spherocytosis.
Ellipsocytosis.
Stomatocytosis.
2. Deficiency of intracellular enzymes.
Glucose-6-phosphate dehydrogenase deficiency
Pyruvat kinase deficiency.
Deficiency of other enzymes.
3. Haemoglobinopathies.
Sickle-cell anaemia.
Thalassaemia.
Other haemoglobinopathies.
4. Acquired haemolytic anaemia.
Auto-immune anaemia.
Paroxysmal cold haemoglobinuria.
Paroxysmal nocturnal haemoglobinuria.
Mechanical destruction of red blood cells.
Toxic (drug) haemolysis.

Supplement II-2

Diseases Marked by the Syndrome of Increased Protein Loss into the Gastro-intestinal Tract

Malignant tumours of any localization.
Coeliac disease-sprue.
Intestinal lymphectasia.
Crohn's disease.
Inflammatory diseases of the large and small intestine.
Hypertrophic gastritis.
Right-ventricular heart failure.
Constrictive pericarditis.
Intestinal lymphogranulomatosis.
Intestinal lymphosarcoma.

Supplement II-3

Causes of Vitamin B_{12} Deficiency

I. Acquired.
1. Gastrinoma.
2. Gastric resection (total, partial proximal).
3. Pancreatitis with secretory insufficiency.
4. Increased vitamin B_{12} consumption in the afferent loop syndrome, dyphyllobothriasis, dysbacteriosis.
5. Affection of the mucous membrane of the terminal ileum (tuberculosis, Crohn's disease, enterocolitis, carcinoma, resection of the terminal ileum, poisoning with alcohol or drugs).
6. Lack of animal proteins in the diet (kwashiorkor, fasting).

II. Congenital.
1. Congenital transcobalamine II deficiency.
2. Groesbeck-Imerslund's syndrome.

Supplement II-4

Causes of Folic Acid Deficiency

Gastric resection complicated by enteritis.
Coeliac disease-sprue.
Primary tumours and ulcers of the small intestine.
Resection of the proximal segment of the small intestine.
Diffuse affection of the small intestine in amyloidosis, scleroderma, Whipple's disease, chronic enterocolitis.
Deficiency of folic acid food sources.

Supplement II-5

Drugs Causing Haemolysis of Red Blood Cells with G6PD Deficiency

Antimalarial agents: quinine, quinacrine, primaquine.
Sulphanilamides: sulphapyridazine (sulphamethoxypyridazine), sulphalen, sulphasalazine, salazopyridazine.
Nitrophuranes: furazolin (furaltadone), furadonin (nitrofurantoin).
Analgetics: acetyl salicylic acid, antipyrin, amidopyrine.
Diuretics: diacarb (acetazolamide), fonurit, thiazides.
Hypoglycaemic agents: tolbutamide (butamide), chlorpropamide.
Antituberculous agents: isoniazid, PAS.
Other agents: chloramphenicol, quinidine, novarsenol (neoarsphenamine), probenecid.

Chapter III

Arrhythmias

Disorders of cardiac rhythm were well known to physicians of the Hellenic period of history. The successes gained in detecting and treating arrhythmias explain the growing interest in this problem today. Disorders of cardiac rhythm are currently encountered and diagnosed much more frequently than in any time in the past. The use of crystal cardiac glycosides in maximum tolerance doses is the principal reason for this. When cardiac glycosides were used in the form of powders and extracts, their toxic effect was easily recognized long before the development of arrhythmias, because it was first manifested by marked gastro-intestinal disorders, namely, anorexia, nausea and vomiting.

Crystal cardiac glycosides are often administered intravenously. When taken orally, they do not cause irritation of the gastro-intestinal tract and the possibility of their overdosage is realized by physicians in our time only when disorders of cardiac rhythm develop.

Modern diagnostic methods allow automatic recording of any disorder in the rhythmic activity of the heart irrespective of its duration and time of appearance. With the application of these methods at the patient's bedside, the true incidence of arrhythmias in some of the diseases was disclosed. It was found that disorders of cardiac rhythm are encountered much more frequently than thought formerly.

Unfortunately, even now arrhythmias are sometimes considered in abstraction from the patient. At the same time, the choice of the therapeutic methods is determined not only by the type of arrhythmia, which can be identified instrumentally, but also by the results of clinical observation over the patient, his condition, how he had suffered attacks of such arrhythmia in the past, and his reaction to the therapy which had been applied.

It is necessary to make a quick and exact diagnosis of arrhythmias, because some types always have a serious prognosis irrespective of their causes, whereas others have no noticeable influence on the patient's fate.

The same type of cardiac rhythm disorder may be a consequence of the activity of different mechanisms. We deem it necessary to point out these mechanisms in brief even from the aspect of differential diagnosis, because in this way we would again remind the physician that the diagnosis of the type of arrhythmia (e.g. atrial

fibrillation) easily made from the ECG does not indicate the mechanism of its development and the prognosis with regard to recovery. The fact that it is impossible to recognize the mechanisms of arrhythmia development from the findings of a routine ECG makes it easier to comprehend the causes of the different efficacy of one and the same agent (e.g. cardiac glycosides) in the same type of cardiac rhythm disorder (e.g. cardiac fibrillation).

Arrhythmias result from simultaneous or separate disorders of cardiac automaticity and conduction (Supplement III-1). In a healthy heart the sinus node possesses maximum automaticity. Its dominance is displayed by inhibition of all the other centres of automaticity. The sinus rhythm of contractions of a healthy heart is evidence of the maintained normal subordination of the centres of its automaticity. When this domination ends under the effect of some cause, conditions are created for the development of arrhythmia. The following two initial mechanisms of its development may be distinguished.

1. Disinhibition of the centres of local automaticity, which are usually inhibited; this occurs when, under the effect of a local lesion or some other cause, the rate of their stimulation exceeds the rate of the sinus node stimulation. In such cases these local centres themselves become the pacemakers of the cardiac rhythm.

2. The underlying factor of the second primary mechanism of arrhythmia is the formation in the heart of a focus or foci of delayed impulse conduction combined with unilateral block of their conduction. In other words, arrhythmia results from impaired conduction with the creation of conditions for circular movement of the impulse or its re-entry into the same myocardial foci.

The standard ECG recorded from the body surface makes it possible to reveal the type of arrhythmia in most, but not in all patients. It usually cannot be determined because the atrial waves and their relation to the ventricular complex cannot be identified. In such cases, besides the usual leads from the body surface, the oesophageal and intraatrial leads from one or two points are used in diagnosing the type of arrhythmia. The His bundle electrograms are now used more widely for this purpose.

The subjective sensations of patients suffering from arrhythmias are very diverse and inconstant. Some patients experience no sensations, while others complain of palpitation and sinking of the heart, i.e. unpleasant feelings occurring in contractions of the heart. Such complaints do not indicate that the disease is serious, but they have a noticeable effect on the patient's emotional state. This fact is well known to all personnel with experience in monitoring such patients.

Some patients have brief attacks of ventricular tachycardia or even ventricular fibrillation without the slightest idea of these ha-

zardous complications, while individuals with increased sensitivity often feel every atrial extrasystole. The unreliability of the clinical method for differentiating various arrhythmias and the general accessibility of electrocardiography justify, as we see it, our discussion of the differential diagnosis of arrhythmias on the basis of the results of this method.

Disorders of Sinus Automaticity

Separate contractions of one and the same healthy heart differ from each other in duration by no more than 0.12 sec. When this value is higher the condition is called sinus arrhythmia. Respiratory (sinus) arrhythmia in which the heart beat rate is increased during inspiration and reduced during expiration, and continuous (sinus) arrhythmia in which the changes in the rate of the heart beat do not depend on respiration, are distinguished. Sinus arrhythmia is asymptomatic.

The rate of cardiac contractions in most healthy individuals ranges between 60 and 100 per minute. In approximately 38 per cent of healthy persons it is less than 60 and in 0.3 per cent higher than 100 per minute. In healthy infants under the age of 12 months the heart beat rate ranges from 110 to 200 per minute. The term 'tachycardia' may evidently be applied unquestionably to an adult only when the heart beat rate exceeds 100 per minute.

The upper boundary of sinus tachycardia depends on the age. The heart beat rate in sinus tachycardia in children may be above 200 per minute. In well-trained young athletes it may be 190 to 200 contractions per minute during peak physical exertion. Sinus tachycardia in peak physical exertion or emotional stress in adults reaches 100 to 150 contractions per minute (depending on age). These data are important in determining the values of maximum and submaximum exertion during electrocardiography undertaken to detect latent coronary insufficiency. This subject is discussed in more detail in the section 'Chest Pain'.

When the heart beat is less than 60 per minute, the condition is called sinus bradycardia. It is often encountered in young healthy persons, particularly in well-trained athletes. It develops regularly during sleep, during vomiting and in other conditions occurring with increased vagal tonus. Sinus tachycardia is observed in many infectious diseases and in approximately 12.5 per cent of patients with myocardial infarction. It is encountered far more frequently in the first hours of infarction in the posterior wall of the left ventricle (in about 41 per cent of patients). Sinus bradycardia always develops in treatment with blocking agents of myocardial β-adrenergic receptors and in toxicosis with potassium drugs.

Extrasystole

The mechanisms of the origin of extrasystoles have not been fully clarified. As it is pointed out by Sumarokov and Mikhailov (1976), extrasystole is always coupled to a preceding normal contraction of the heart in timing and this coupling is firmly fixed. Early extrasystoles occur no later than 0.04 sec after a sinus contraction. Other authors interpret this 'bigeminy rule' more condescendingly and allow that the interval of time between the normal contraction and the early extrasystole may be much longer.

Atrial extrasystoles are encountered very frequently. Emotions, fatigue, alcohol, coffee and tobacco may precipitate them even in healthy persons. The detection of atrial extrasystoles in 0.4 per cent of healthy males between the ages of 16 and 50 may possibly be attributed to the influence of these factors. Atrial extrasystoles are encountered much more frequently in heart diseases. They are observed particularly often in distension of the atrium, e.g. in mitral stenosis, in ischaemia, e.g. in atherosclerotic cardiosclerosis, myocardial infarction as well as in focal dystrophies, e.g. in thyrotoxicosis.

Atrial extrasystoles are usually asymptomatic, but sometimes patients complain of palpitation or sinking of the heart. If an extrasystole occurs before the tricuspid valve opens, the blood from the atrium is ejected into the venae cavae. This ejection may be recorded as a positive pulse wave in the jugular vein. The sinus node is incompletely discharged by the atrial extrasystole and the compensatory pause is therefore shorter after the atrial extrasystole than after the ventricular systole almost in all cases. These clinical signs of atrial extrasystole can rarely be detected at the patient's bedside, unfortunately, and its diagnosis may therefore be made with confidence only from the ECG findings.

The principal electrocardiographic sign of atrial extrasystole is premature appearance of the atrial wave which is followed by a ventricular complex of a normal or slightly altered shape. The atrioventricular conduction is normal or slightly delayed. An extrasystolic atrial wave superimposed on the *T* wave of the preceding normal contraction is often detected with difficulty. Atrial extrasystoles which are not transmitted to the ventricles are recognized by the changed shape of the *ST-T* complex and the following, usually incomplete, compensatory pause.

Atrioventricular extrasystoles. Cells capable of being pacemakers are localized in His' bundle and at its junction with the atrioventricular node but not in the node itself (Hoffman and Cranefield, 1964). Extrasystoles arising in these cells are conditionally called atrioventricular. They are encountered in only 0.2 per cent of healthy

males of 16 to 50 years of age. They are detected comparatively rarely in diseases of the heart.

Impulses arising at the junction of His'bundle and the atrioventricular node spread simultaneously both to the atria and to the ventricles. Depending on the rate of the spread of impulses and the site of their origin, the atria may be stimulated at the same time as, later or before, the ventricles. An atrioventricular extrasystole causes the appearance of a large pulse wave on the jugular vein. The first cardiac sound is flapping in early contraction of the atria and diminished in all other cases.

Atrioventricular extrasystoles are diagnosed on the ECG by the retrograde atrial wave which is always negative in leads II, III and aVF and positive in lead aVR. The atrial wave in lead I is almost always isoelectric. In the right chest leads the atrial waves are either positive or biphasic, while in the left chest leads they are slightly negative. The initial part of the ventricular complex is usually normal in shape. Nodal extrasystoles occur if the impulse from the junction of the atrioventricular node and His'bundle is conducted only in the direction of the ventricles.

Ventricular extrasystoles are the most common form of arrhythmias both in healthy and in sick persons. They were recorded on the ECG of 0.8 per cent of healthy males aged from 16 to 50. Monitor findings indicate that they are encountered in 40 to 80 per cent of cases with acute myocardial infarction. They are very often encountered in other heart diseases. Ventricular extrasystoles are asymptomatic in many cases. Sometimes patients complain of a brief stopping of the heart, palpitation and even brief pain which is referred to the neck. Comparison of the pulse rate with the number of cardiac contractions reveals a pulse deficit which is detected by a loss of some of the pulse waves on a peripheral artery.

An extrasystole arising from the ventricular wall is diagnosed on the ECG by a premature broad, usually notched, *QRS* complex. If the extrasystole arises from a focus in the ventricular septum in the vicinity of the bifurcation of the His bundle, the *QRS* complex is slightly broadened and only mildly deformed. The *ST-T* complex is usually directed in an opposite way to that of the main deflection of the initial part of the ventricular complex. As it is noted above, a ventricular extrasystole usually occurs at equal intervals after a preceding normal contraction.

In some cases, ventricular extrasystoles help to overcome difficulties in identifying cardiac sounds and murmurs. A systolic murmur of aortic stenosis is often transmitted to the heart apex where it is sometimes mistaken for the systolic murmur of mitral insufficiency. During a heart contraction beginning immediately after the compensatory pause, the systolic murmur of aortic stenosis is noticeably intensified while the intensity of a systolic murmur

of mitral insufficiency remains unaltered. Sharp diminution or even disappearance of diastolic murmur during the compensatory pause is encountered only in cases with mild mitral stenosis.

The configuration of the ventricular extrasystole on the ECG is also of high diagnostic significance in some cases. Ventricular extrasystoles traced on wave *T* of the previous contraction ('*R* on *T*' phenomenon) also indicate the possible development of ventricular tachycardia or ventricular fibrillation. Bundle branch block prevents the demonstration of electrocardiographic signs of myocardial infarction which, however, often become manifest in the first post-extrasystolic ventricular complex.

In severe atrial tachycardia with block of every second contraction, abnormal *P* waves often coincide with the *T* wave and become unidentifiable. During the compensatory pause following the ventricular extrasystole, two successive *P* waves may sometimes be distinguished. Thus, ventricular extrasystoles sometimes considerably help in the diagnosis of some heart diseases.

Supraventricular Tachycardia

Ectopic tachycardia occurring above the bifurcation of the His bundle is called supraventricular. This group includes atrial and atrioventricular types of tachycardia. Atrial fibrillation and flutter are usually set apart as a special group. Identification of these rhythm disturbances both by clinical manifestations and by the results of ordinary ECG is often an exceptionally difficult and at times an impossible task. In typical cases the final diagnosis may be made at the patient's bedside.

Attacks of supraventricular tachycardia are sometimes asymptomatic, but usually the patients complain of palpitation. The rate of cardiac contractions during the attacks ranges in most cases between 160 and 220 per minute. The cardiac rhythm is almost always normal and the force of the first heart sound is therefore distinguished by typical constancy on condition that the patient is auscultated when he holds his breath. During short attacks the cardiac rhythm may be irregular, which is demonstrated by an inconstant force of the first sound. The occurrence of a block, usually of the right branch of the His bundle, is manifested by splitting of the first heart sound. Pulsation of the veins on the neck is observed in severer and longer attacks. Marked polyuria sometimes occurs at the beginning or end of the attack. A sudden increase in the vagal tonus often stops an attack of tachycardia.

The contingent of persons suffering from supraventricular tachycardia may be divided into two groups. The first consists of individuals in whom routine clinical examination does not reveal any lesion of the heart. The second group includes patients with rheu-

matic heart diseases, the Wolff-Parkinson-White syndrome, and myocardial infarction.

Supraventricular tachycardia (its paroxysmal atrial form) in combination with complete or incomplete atrioventricular block often develops in overdosage of cardiac glycosides. Cases with such tachycardia unassociated with cardiac glycoside toxicosis are very rare. The therapeutic tactics in this form of supraventricular tachycardia is determined by the degree of the atrioventricular block which may be judged only by the ECG.

The focus of heightened automatism in this form of arrhythmia is usually localized close to the sinus node, and the atrial waves of the ECG are therefore positive. They follow one another at a constant rate. The ventricular complexes (like in other forms of supraventricular tachycardia) are unchanged. The rate of automatism in the ectopic focus is so high that only some of the atrial impulses are conducted to the ventricles. Atrioventricular block of type 2:1, 3:1 and 4:1 is usually encountered. Complete block develops in rare cases.

Paroxysmal atrial tachycardia with atrioventricular block has to be differentiated mostly from atrial flutter. The former usually occurs in severe cases with signs of heart failure for which the patient is given cardiac glycosides. Atrial flutter often develops in individuals with no heart failure. The compared forms of tachyarrhythmia differ in the shape of the atrial wave which is almost normal in atrial tachycardia and always considerably broadened in atrial flutter. The rate of performance of the ectopic centre is much higher in atrial flutter than in atrial tachycardia.

During attacks of supraventricular tachycardia a good part of the blood accumulates in low-pressure vessels. This is clinically manifested by increased blood filling of the lungs with the development of pulmonary infarcts in severer cases. Most patients who do not have chronic heart diseases tolerate even long-term attacks of supraventricular tachycardia well. Marked shortening of the diastole in severe tachycardia in patients with coronary atherosclerosis and rheumatic heart diseases may lead to the development of coronary insufficiency or to a sharp decrease of the cardiac debit. This is manifested clinically by pain in the region of the heart, sharp fall of arterial pressure, hepatomegaly, and increased venous pressure in systemic and pulmonary circulation.

It is general knowledge that some of the modern anti-arrhythmic agents predominantly affect the conduction of impulses in the atrioventricular node, while others affect the conduction of impulses in the myocardium and accessory pathways connecting the atria and ventricles and by-passing the atrioventricular node. One of the conditions for effective treatment of different forms of supraventricular tachycardia, therefore, consists in establishing the mech-

anism of their development. The form of supraventricular tachycardia cannot be determined from the clinical picture.

It was established in the last decade that if tachycardia begins with atrial extrasystoles while the impulse to the ventricles is conducted through the atrioventricular node, the configuration of the *QRS* complex on the ECG remains unchanged. It is always changed, however, when tachycardia begins with an atrial extrasystole, while the impulse to the ventricles is conducted through the accessory pathways and re-enters the atria retrogradely through the atrioventricular node. This is often accompanied by block of the anterior segment of the left branch alone or in combination with the right bundle branch block.

In some cases the accessory conduction pathways of the heart are only capable of retrograde conduction of impulses from the ventricles to the atria (Narula, 1974). The attacks of supraventricular tachycardia occur in these patients without the formation of the delta wave and without shortening of the *PQ* segment on the ECG.

Supraventricular tachycardia is easily diagnosed from the ECG if an ectopic though not a retrograde atrial wave can be detected before each ventricular complex of normal or broadened configuration. If a broadened *QRS* complex is preceded by a negative atrial wave, then the electrocardiographic criteria do not allow supraventricular tachycardia to be distinguished from ventricular tachycardia with retrograde impulse conduction from the ventricles to the atria.

A diagnosis of atrioventricular tachycardia may be made only when the beginning and the end of the attack are recorded on the ECG and when it can be established that the first or the last ventricular complex is attended by a retrograde atrial wave traced before or after the *QRS* complex. Atrioventricular tachycardia is also diagnosed when simultaneously with unchanged *QRS* complexes the ECG shows *P* waves which are independent of them or records fibrillation.

The diagnosis of an atrial form of supraventricular tachycardia is made with confidence when changed *P* waves are clearly distinguished before each ventricular complex. When these waves are clearly identified they may be easily differentiated from atrial waves of sinus origin. They may be positive, but in this case they differ from atrial waves of sinus origin in configuration. If negative, they cannot be distinguished from negative atrial waves occurring in retrograde spread of the impulse through the atrioventricular node. When the ventricular complexes have a normal configuration and the atrial waves are unidentifiable or negative, then tachycardia may be atrial, atrioventricular (with retrograde conduction of impulses from the His' bundle to the atria) or caused by a reciprocal rhythm.

Atrial Flutter and Fibrillation

Attempts to elaborate differential diagnostic criteria between **atrial flutter** and atrial tachycardia on the grounds of the differences in atrioventricular conduction, rate of contractions, configuration of the atrial waves on the ECG, and the response to stimulation of the vagus nerves, failed. Bearing in mind that these tachycardias cannot be strictly distinguished, tachycardia with the atrial contraction rate ranging from 200 to 400 (mostly from 270 to 330) per minute and with each second contraction usually conducted to the ventricle is conditionally regarded as atrial flutter.

An ECG recorded prior to flight showed flutter of the atria in one of 67 000 pilots between the ages of 16 and 50 who had no complaints. Though this form of tachycardia may be asymptomatic, it is nevertheless attended by complaints of palpitation as a rule. Atrial flutter is usually encountered in patients suffering from myocardial infarction and atherosclerotic cardiosclerosis. In some cases it is induced by quinidine, procaine amide, and cardiac glycosides prescribed for treating cardiac fibrillation. Brief attacks of atrial flutter often occur in elderly and old individuals during acute diseases (influenza, pneumonia, pulmonary or myocardial infarction).

In some cases with atrial flutter the ventricles contract with a normal rhythm. These patients make no complaints, while clinical examination reveals pulsation of the external jugular veins and regular tachycardia with a heart beat of 150 to 160 per minute, which is in no way different from supraventricular tachycardia. Sharp increase in the vagal tonus is attended by short-term deceleration of the heart beat and often also by disorders of the rhythm of cardiac contractions. The rate of the heart beat usually reduces by half or more, e.g. from 160 to 80 per minute. This phenomenon, like the disorder of cardiac rhythm, is explained by disturbed conduction in the atrioventricular node.

Atrial flutter is usually marked by conduction of every second atrial contraction to the ventricles. Every fourth impulse is conducted much less frequently, while tachycardia in which every third or fifth or two of three atrial contractions are conducted to the ventricles is still rarer. From time to time every atrial contraction is conducted to the ventricles. This should be borne in mind in every case of tachycardia with a heart beat rate of about 300 per minute. Fluctuation in impulse conduction is attributed to the development of Wenckebach's phenomenon in the atrioventricular node.

The atrial waves traced on the ECG in atrial flutter usually have a sawtooth appearance. They are best demonstrated in leads II, III and aVF and the right chest leads. In rare cases *P* waves

are demonstrated only in the right chest leads or are clearly seen in leads from the limbs but are indistinct in the right chest leads. In conduction of every second impulse to the ventricles, the second *P* wave is often superimposed onto the ventricular complex, in which case atrial flutter may only be suspected or stays unrecognized.

The true cause of tachycardia in such instances may be easily disclosed by exerting pressure on the eyeballs or the carotid sinus. The conduction of every second impulse recorded on the initial ECG is replaced by the conduction of every third, fourth or fifth impulse when pressure is applied to the carotid sinus. As soon as stimulation of the vagus nerve ceases, this phenomenon disappears.

Cardiac fibrillation is characterized by complete loss of atrial systoles. The rhythm of ventricular contractions is always abnormal. The rate of the heart beat is determined by the condition of conduction in the atrioventricular node. Paroxysmal and permanent forms of cardiac fibrillation are distinguished. They are both related to the group of common arrhythmias. They may be encountered in some individuals who regard themselves to be quite healthy. Cardiac fibrillation is a frequent complication of mitral stenosis, atherosclerotic cardiosclerosis, thyrotoxicosis, atrial septal defect, and constrictive pericarditis. Monitoring data show that it is encountered in 7 to 16 per cent of cases with acute myocardial infarction.

Cardiac fibrillation predisposes to the development of heart failure and the formation of thrombi in the heart cavities. Approximately one third of patients with long-term cardiac fibrillation prove to have suffered embolism of arteries of the systemic or pulmonary circulation once or twice. Patients with cardiac fibrillation usually complain of palpitation, oedema, dyspnoea, haemoptysis or disorders in the function of internal organs caused by embolism. Examination usually discloses one of the diseases listed above. The changing depth of the first heart sound and a pulse deficit are among the most valuable clinical signs of cardiac fibrillation. They are constant findings in this disease, but may also be encountered in other disturbances of the cardiac rhythm. The final diagnosis of cardiac fibrillation may be established only from the ECG.

The waves arising in atrial fibrillation are best demonstrated in lead V_1. They are usually identifiable in leads II, III and aVF but are rarely clear in leads I and aVL. The ventricular complex is usually normal in configuration, although aberrant ventricular complexes may be encountered which are sometimes mistaken for ventricular extrasystoles.

An aberrant ventricular complex combined with a preceding normal complex always forms a dual consisting of a long-term cardiac cycle followed by a short cycle. The initial vector of the aberrant

complex is always directed in the same way as the initial vector of the preceding ventricular complex. Electrocardiographic signs of right bundle branch block with the *rsR'* complex in lead V_1 are almost a constant sign of an aberrant ventricular complex and are not encountered in ventricular extrasystoles. A series of successive aberrant ventricular complexes may be mistaken for a brief attack of ventricular tachycardia. The decision concerning this diagnostic problem determines the choice of the therapeutic measures at the patient's bedside.

Ventricular Tachycardia

A series of three or more ectopic ventricular contractions following one another at a rate exceeding 100 per minute is diagnosed as an attack of ventricular tachycardia. The rate of ventricular contractions ranges in most cases between 150 and 200 per minute. It is generally accepted that an attack of ventricular tachycardia is a sign of affection of the heart. This assumption is also confirmed by the results of examination of healthy individuals. A series of three consecutive ventricular contractions occurring at the rate pointed out above was recorded in only one of more than 67 000 males of 16 to 50 years of age who had no complaints.

Among patients with ventricular tachycardia, 71 to 73 per cent had ischaemic heart disease and 8 to 12 per cent rheumatic heart diseases. According to the results of monitoring, ventricular tachycardia is encountered in 6 to 28 per cent of cases with acute myocardial infarction. Cases have been described in which ventricular tachycardia was induced by catheterization of the heart, cardiac glycosides, anti-arrhythmic and other agents. It sometimes occurs in individuals with no clinically apparent signs of a heart disease. Such cases may be explained by the existence in the heart of accessory conduction pathways with retrograde conduction of impulses.

An attack of ventricular tachycardia is usually attended by a sharp fall in arterial pressure and pain in the region of the heart. Soon after the attack begins, signs of left-ventricular failure appear, often with pulmonary oedema, right-ventricular failure with enlargement of the liver, and sometimes shock develops also. Stimulation of the carotid sinus does not cause heart beat deceleration. When every ventricular impulse is conducted to the atria, every atrial contraction is attended by visible pulsation of the neck veins. The force of the first sound in this form of ventricular tachycardia remains constant during the entire attack.

In combination of ventricular tachycardia with cardiac fibrillation, the force of the first sound remains unchanged during the attack but there is no pulsation of the veins on the neck. The force

of the first sound changes continuously when the ventricles and atria contract irrespective of each other. Splitting of the first heart sound and a gallop rhythm are encountered in all forms of ventricular tachycardia.

The *QRS* complex in ventricular tachycardia is always broadened but its configuration is in no way different from that in a ventricular extrasystole. The existence of two independent rhythms, atrial and ventricular, is detected in approximately 20 per cent of cases with ventricular tachycardia. Retrograde atrial waves are very rarely identified. In some cases of ventricular tachycardia with a heart beat below 150 per minute, transitional complexes from ventricular to synoatrial are recorded on the ECG, besides the typical ventricular complexes. A close form is ventricular tachycardia occurring as a series of attacks separated from each other by several contractions arising from the sinus node.

Ventricular tachycardia has always to be differentiated from supraventricular tachycardia with an aberrant *QRS* complex. The simplest way to do this is to use oesophageal or intracardiac leads. The demonstration of positive atrial complexes preceding the ventricular complexes leaves no doubt that the tachycardia is of supraventricular origin.

Analysis of the configuration of the ventricular complexes makes differential diagnosis much easier. A high *R* wave in lead v_1 (as *rsR'*, *qR* or *R*) is only encountered in supraventricular tachycardia with delayed conduction of the impulse to the ventricles. In other chest leads the *R* waves are usually also high. The atrial waves in supraventricular tachycardia are concealed in the broadened and usually deformed *QRS* complex. Pressure applied to the eyeballs or the carotid sinus delays the conduction of the impulse from the atrium to the ventricle as a result of which the *P* wave separates from the *QRS* complex and becomes clearly visible. Intravenous infusion of anti-arrhythmic agents, for instance novocaine amide, is sometimes used for this purpose. Deceleration of atrioventricular conduction by these agents is attended by separation of the atrial waves from the ventricular complexes on the ECG.

Temporary delay of intraventricular conduction is sometimes encountered in cardiac fibrillation. The series of aberrant ventricular complexes in such cases may be mistaken for an attack of ventricular tachycardia. They may be easily distinguished from ventricular tachycardia if the beginning and end of the attack are recorded. Aberrant complexes may also occur in supraventricular tachycardia. They always have a configuration typical of right bundle branch block and begin after a cardiac cycle which is longer than usual, and there is no compensatory pause after they end. Ventricular tachycardia must also be differentiated from tachycardia in the Wolff-Parkinson-White syndrome.

Wolff-Parkinson-White Syndrome

The Wolff-Parkinson-White syndrome, first described by Wilson in 1915, comprises three signs: shortening of atrioventricular conduction, appearance of delta waves or sawtoothed tracings on the ascending part of the *QRS* complex, and attacks of tachyarrhythmia. The underlying factors of the syndrome may be a shorter than normal atrioventricular node, or the presence of two nodes noticeably differing from each other in the rates of impulse conduction (Rosen et al., 1974), or the presence of accessory pathways for impulse conduction from the atria to the ventricles by-passing the Aschoff-Tawara node along the muscular bundles: atrioventricular (Kent's bundle), intraseptal (Palladino's bundle), nodularventricular (Mahaim's bundle) and atrio-His' (James' bundle).

In 1954 the Wolff-Parkinson-White syndrome was separated into type A (with positive) and type B (with negative delta waves). Between these extreme types are very many transitional types which make the classification very difficult.

The attacks of tachycardia in the Wolff-Parkinson-White syndrome begin with atrial or ventricular extrasystoles. The atrial extrasystoles spread to the ventricles either through the atrioventricular node or through the accessory conduction pathways. The *QRS* complex will be normal in the first case, but broadened in the second. The ventricular extrasystoles spread to the atria retrogradely. The *QRS* complex in this type of tachycardia is always broadened and its configuration is changed.

The predisposition of patients with the Wolff-Parkinson-White syndrome to tachyarrhythmias is a well-known fact. Most of these arrhythmias are supraventricular. The mechanism of their origin has not been fully comprehended. No explanation has been found, for instance, for the fact that atrial extrasystoles are encountered more often in patients with this syndrome than in healthy individuals. According to some data, atrial tachycardia is most common in patients with the Wolff-Parkinson-White syndrome (in 70 per cent of cases); 16 per cent falls to the share of cardiac fibrillation, and 4 per cent of cases accounts for atrial flutter. In the remaining 10 per cent of cases, the supraventricular tachycardias prove to be unidentified.

The *QRS* complex in patients with the Wolff-Parkinson-White syndrome is almost always broadened and the occurring supraventricular tachyarrhythmias may therefore be mistaken for ventricular tachycardia. When considering the differential diagnosis between these syndromes, it is necessary, whenever possible, to find the patient's ECGs, which had been recorded formerly, and make a careful study of the configuration of the *QRS* complex traced on them.

The rate of cardiac contractions rarely exceeds 200 per minute in ventricular tachycardia, but is usually higher in supraventricular tachyarrhythmias. A notch on the ascending limb of the *QRS* complex suggests the presence of the Wolff-Parkinson-White syndrome, but does not prove its existence because a similar deformity of the *QRS* complex is sometimes encountered in ventricular tachycardia. Intracardiac ECG leads (from the upper and lower parts of the atrium, from the His bundle) provide the possibility for studying the passage of the stimulation wave in the heart and identifying the source of the stimulation. This method of examination has not been given wide application as yet.

Other Arrhythmias

The term **sinus node depression** syndrome designates any sharply pronounced sinus bradycardia, sinoatrial block and short-term arrest of sinus node automaticity which are not associated with vagotonia or the effect of any drug. Some authors call it the sinus node dysfunction syndrome, others the sick sinus syndrome and still others the tachycardia-bradycardia syndrome. The last designation emphasizes the principal feature of the clinical manifestations of this form of arrhythmia, namely, a tendency to a frequent change in the rate of cardiac contractions.

It is common knowledge that the arrest of sinus automaticity in a healthy heart is attended by increased automaticity of its lower localized centres, increased automaticity of the atrioventricular node in the first place. During long-term depression of the sinus node in the discussed form of cardiac rhythm disorder, the centres of automaticity localized at a lower level are also depressed and incapable of controlling the rhythm of cardiac contractions.

The syndrome is manifested by paroxysms of supraventricular tachycardia (and often by cardiac fibrillation) which are followed by more or less long periods of marked sinus bradycardia. Depending on the duration of the asystolia periods, patients have dizziness, syncope or Morgagni-Adams-Stokes attacks. Milder cases of the syndrome follow an asymptomatic course for a long time. Depression of the sinus node is encountered in the acute period of myocardial infarction, in atherosclerotic cardiosclerosis, myocarditis and cardiomyopathies.

Delayed Atrioventricular Conduction

Three degrees of delayed atrioventricular conduction are distinguished. In the first degree delay all impulses from the atria reach the ventricles at a rate lesser than normal. In the second degree

delay some of the atrial impulses do not reach the ventricles. When none of the atrial impulses reach the ventricles, the condition is called third degree delayed atrioventricular conduction or total atrioventricular block.

In appraising the patient's condition it should be borne in mind that the severity of the disturbance in automaticity and conduction is determined by the rate of atrial and ventricular contraction and not by the degree of the block. Type 2:1 block in sinus node automaticity of 70 impulses per minute is encountered only in severe disorders of atrioventricular conduction, whereas this type of block in paroxysms of atrial tachycardia with the automaticity of an ectopic focus of 200 impulses per minute may sometimes simply be evidence of the frequently encountered functional block of impulses in the atrioventricular node.

According to the results of mass-scale screening, *first degree atrioventricular block* is revealed in 0.5 per cent of practically healthy flight personnel from 16 to 50 years of age and in 0.3 per cent of young applicants to flying schools. It is usually asymptomatic. It is diagnosed on the ECG in all cases when the duration of the *PQ* interval exceeds 0.21 second.

It is accepted that an increase in the rate of cardiac contractions is attended by shortening of the *PQ* interval on the ECG. If one takes this view it is necessary to bear in mind that it is only true of a healthy heart. In cardiac patients with an increased rate of cardiac contractions, the *PQ* interval is not shortened but, on the contrary, increased. This regularity is demonstrated more clearly if the *PQ/QR* ratio is determined and not simply the duration of the *PQ* interval.

Second degree delayed atrioventricular conduction with Wenckebach's pauses is exceptionally rare among healthy individuals (it has been registered in 3 of 67 000 practically healthy males). It may be induced by vagal stimulation, cardiac glycosides and antiarrhythmic agents. It is sometimes encountered in rheumatic fever, myocardial infarction, atherosclerotic cardiosclerosis, myocarditis, thyrotoxicosis, Addison's disease, congenital heart diseases and in hypoxia of any origin. In most cases second degree atrioventricular block with Wenckebach's pauses produces no symptoms, prevails for some time and then disappears leaving no trace. According to the findings of intracardiac electrography, atrioventricular block with Wenckebach's pauses results from delayed conduction of the impulse in the atrioventricular node.

Type II atrioventricular block with dropping of occasional ventricular contractions and no preceding prolongation of the *PQ* interval is encountered in severer affections of the heart. Once it appears, it usually remains, and often, with time, develops into a constant block. According to the results of intraventricular electro-

graphy, type II block is a consequence of a lesion of the His bundle or its main branches (Domato and Lau, 1970). This type of block is clinically manifested by dizziness and sometimes also by syncope.

When the atria and ventricles contract irrespective of each other, the condition is called *complete atrioventricular block.* It may be congenital or acquired. When the centre of ventricular automaticity is above the bifurcation of the His bundle, the configuration of the *QRS* complex is normal, but if this centre is localized in the ventricles, the *QRS* complex is broadened and its configuration is altered. Two or more alternately functioning pacemakers are sometimes found in the ventricles.

Complete atrioventricular block may be asymptomatic, but usually the patients complain of palpitation, dizziness and syncope, which are sometimes attended by convulsions. The appearance of convulsions is determined by the duration of the asystolic period. The rate of ventricular contractions is below 50, as a rule, and often 40 per minute. A systolic murmur is heard in all cases of complete atrioventricular block. A very loud sound is heard when atrial systole immediately precedes ventricular systole. During some of the systoles the arterial pressure may vary.

It is traditionally believed that the underlying factor of complete atrioventricular block is ischaemic heart disease. The block is often encountered, however, in individuals who have no signs of this disease. In generalizing these observations Lenegre (1967) postulated the thesis on the existence of a primary disease of the heart conduction system. The disease is encountered in elderly and old individuals who have no signs of atherosclerosis of the coronary arteries. The right branch or the anterior limb of the left branch of the His bundle is involved at first. Complete atrioventricular heart block develops when fibrosis spreads to the whole branch (Balcon, 1973).

The second cause of complete atrioventricular block is calcification of the mitral valve fibrous ring; on progressing the calcification involves the adjoining branches of the heart conduction system. It was shown that fibrosis or calcification of the connective tissue ring of the mitral valve is the most common cause of complete atrioventricular block with normal configuration of the *QRS* complex in elderly and old individuals. Only a small number of cases of complete atrioventricular block fall to the share of ischaemic heart disease. Complete atrioventricular block must be suspected in all patients with a rate of heart beats less than 50 per minute. Such a suspicion seems all the more justified if the patient complains of dizziness or syncope in addition, and very loud heart sounds are heard. The final diagnosis is made from the results of electrocardiography. The site of the block is determined from intracardiac electrograms.

Supplement III-1

Major Types of Arrhythmia

1. Sinus arrhythmia.
2. Extrasystole (ectopic beats).
   - Atrial extrasystole.
   - Atrioventricular extrasystole.
   - Ventricular extrasystole.
3. Supraventricular tachycardia.
4. Atrial flutter and atrial fibrillation.
5. Ventricular tachycardia.
6. The Wolff-Parkinson-White syndrome.
7. Sinus node depression (sick sinus syndrome).
8. Delayed atrioventricular conduction.
   - First degree (with Samoilov-Wenckebach's pauses).
   - Second degree (with dropping of occasional contractions).
   - Complete atrioventricular block.

Chapter IV

Arterial Hypertension

Arterial pressure gradually increases with age. In the newborn it is approximately 75/40 mm Hg, in adolescents 100/65 and in adults 140/90 mm Hg. According to the recommendation of WHO experts, the normal top value of arterial pressure is 160/95 mm Hg. Arterial hypertension is spoken of when the blood pressure in the brachial artery repeatedly measured under conditions of basal metabolism exceeds these values for a long time.

Systolic hypertension caused by increased minute volume or arterial rigidity and diastolic hypertension resulting from increased vascular resistance to blood flow at the level of the arterioles are distinguished. The systolic and diastolic forms of hypertension usually occur in conjunction, though they may also exist separately. Arterial hypertension is designated symptomatic when its cause has been identified, and essential (idiopathic) hypertension, or hypertensive disease, when its cause cannot be determined.

According to the level of arterial pressure and the course followed by the disease, arterial hypertension is divided into benign and malignant. Benign hypertensive disease is the most prevalent type of arterial hypertension today. According to some data, it accounts for 77.2 per cent of all cases with arterial hypertension.

The causes of hypertensive disease have not been ultimately established. Myasnikov (1965) contended that the underlying factor of hypertensive disease is neurosis, as the term is interpreted by Pavlov. According to this hypothesis, the principal aetiological factor of hypertensive disease is psychoemotional overstrain leading to impaired regulation of the vascular tone. In its time this hypothesis was supported by many firm adherents. In recent years it has noticeably lost in popularity. Although not refuting the effect of habitation environmental factors and genetic predisposition many contemporary clinicists regard essential hypertension as a disease of uncertain origin.

For some time, arterial hypertension may produce no subjective sensations of illness and no objective signs of disturbances in the structure and function of organs. The disease may only be revealed then by measuring the level of arterial pressure. It should be borne in mind in such cases that its moderate increase may at times occur in healthy persons, which is generally regarded as a reaction of the patient to an unusual situation. Measurement of arterial pressure

for the first time in life is without any doubt such a situation. Only the results of more or less prolonged observation over the patient will enable the physician to distinguish persistent arterial hypertension from these short spans of increased pressure due to some situations in healthy individuals.

Long-term hypertension, even if it is moderate, leads to characteristic changes in the vessels of the brain, heart and kidneys. Correct appraisal of these changes sometimes allows arterial hypertension to be distinguished during the very first examination of the patient from increased arterial pressure induced by certain circumstances.

Headache is regarded among the characteristic symptoms of arterial hypertension. It is often the only symptom and is usually of a pulsating character and is felt at the back of the head. Headache may occur even with a mild increase of arterial pressure. It acquires diagnostic significance only when it appears often or almost regularly in the morning, then gradually abates and disappears completely or almost completely by dinner-time. Such typical headache is encountered in no more than 25 per cent of patients and only when the diastolic arterial pressure rises above 100-110 mm Hg.

In cases with comparatively recent and mild hypertension, the cerebral vessels, the condition of which is judged by the results of ophthalmoscopy, prove to be normal. With advancement of the disease changes in the vessels develop. At first they are mild, inconstant, and displayed by constriction of the arteries, dilation of the veins and a pale optic papilla. Punctate extravasations are detected in the retina later. The walls of the small arteries of the fundus oculi are usually sclerosed by this time.

The left ventricle of the heart counters the increased resistance in arterial hypertension. This leads to its hypertrophy which is manifested at first by intensified apex beat, rounded left-ventricular apex and characteristic ECG changes.

Smolensky and later other authors established that arterial hypertension is one of the factors promoting earlier development of atherosclerosis of the coronary arteries. Consequently, the heart mass increases at the very onset of arterial hypertension, while the conditions for its blood supply deteriorate. This disparity between the requirements of the heart in blood and the possibilities of meeting them becomes more and more obvious with the advancement of the disease and leads to the development of latent heart failure. According to some data, latent heart failure begins in the early stages of hypertensive disease. It has also been suggested that patients with arterial hypertension should be looked upon as individuals with a potential heart disease. Prompting the development of atherosclerosis, arterial hypertension in the elderly may be one of the factors disclosing coronary insufficiency. Pain in the area

of the heart is of small significance in the diagnosis of arterial hypertension.

Affection of the kidneys in arterial hypertension is at first displayed by impairment of their concentration and dilution functions. Traces of protein are found in the urine somewhat later. Nycturia and polyuria already point to functional insufficiency of the kidneys. The other symptoms of renal insufficiency (nausea, vomiting, skin itch) are important in evaluating the severity of arterial hypertension rather than in making the diagnosis, because they are only found in cases of drastically pronounced arterial hypertension which is usually irreparable by that time. The same is true of the symptoms of encephalopathy.

The late appearance of the characteristic complaints and objective signs indicating the affection of internal organs makes early diagnosis of arterial hypertension very difficult. Just as frequent blood tests for haemoglobin simplify timely diagnosis of mild anaemias, repeated measurement of arterial pressure during prophylactic surveys and examination of out-patients for other diseases constitutes the most reliable method of the early diagnosis of arterial hypertension.

After arterial hypertension has been disclosed it is necessary to become assured that it is of stable character. As soon as the diagnosis of arterial hypertension becomes obvious the question of its aetiology arises. As it was noted above, the aetiology of arterial hypertension in most cases remains uncertain. Supplement IV-1 lists the causes of symptomatic hypertension among which that of renal origin is most common.

The special interest evoked by the rare forms of symptomatic hypertension is attributed to the fact that some of them are potentially curable. The fate of the patient in such cases depends on the physician's clinical perception, his ability to identify the correct diagnosis among many plausible variants. The diagnosis of hypertensive disease is only made when all other diseases complicated by the hypertensive syndrome are ruled out.

Hypertensive Disease

Most cases of hypertensive disease now take a benign course. Interrogation of all patients with benign hypertensive disease yields information on a very characteristic medical history. The first short-term and moderate elevations of arterial pressure are often encountered in puberty. Arterial hypertension becomes stable between the ages of 30 and 35 as a rule. In the following 15 to 20 years the disease is distinguished by a benign course. The basal arterial pressure is always considerably lower than that at the end of the work-

ing day. As a result of hospital stay, arterial pressure drops noticeably, quite often even to normal values. Despite the increased arterial pressure these patients usually have no subjective disturbances of health, which provided grounds for designating this period of the disease 'silent hypertension'. In the second half of this period, hypertensive crises may occur. The signs of affection of the cardiac and cerebral vessels described above, usually mild, are found at the age of about 45 to 50.

Progressive development of the disease slows down after this age is reached. Arterial pressure stabilizes at a certain level or begins decreasing gradually. Hypertensive crises become less and less frequent and milder. In the elderly, the diastolic pressure begins to drop, the systolodiastolic hypertension 'undergoes sclerosis' and changes to systolic. Benign hypertensive disease begins very rarely after the age of 50.

Malignant hypertensive disease sets in acutely usually between the ages of 20 and 50. High-level hypertension occurs from the very start. The diastolic pressure rises particularly sharply, often reaching 120-150 mm Hg. Hypertension is at the same high levels at night as in the early morning hours. Changes in the fundus oculi appear at the onset of the disease. Oedema of the optic papillae and retina and extravasation into the retina often with disorders of vision to total blindness are considered typical signs.

Among the early finding is hypertensive encephalopathy with characteristic headache, vomiting and bradycardia which, together with oedema of the optic papillae, may simulate tumour of the brain. Memory and working capacity are drastically diminished.

Early appearance of left-ventricular failure with attacks of cardiac asthma and pulmonary oedema is characteristic. A diastolic murmur of aortic insufficiency sometimes appears during such attacks and disappears a few days after the attack. This distinguishes it from diastolic murmur of aortic insufficiency occurring often in patients with malignant hypertensive disease complicated by uraemia.

We feel it necessary to emphasize that not a single one of our patients with malignant hypertensive disease developed either arrhythmias or myocardial infarction even after recurrent acute pulmonary oedema. In some cases just before death right-ventricular failure occurred in addition to left-ventricular failure, which resulted in enlargement of the liver and the appearance of oedema and ascites.

Systemic affection of the vessels in malignant hypertensive disease usually occurs with involvement of the kidneys which begins with mild proteinuria. Haematuria soon develops also. The content of non-protein nitrogen in blood begins increasing several months

after proteinuria develops. Massive renal haematuria is observed in rare cases. The irrepressible increase of azotaemia is a characteristic symptom and death usually occurs three or four months after its onset. Patients with malignant hypertensive disease die mostly from haemorrhage into the brain before the appearance of azotaemia or from heart failure in mild azotaemia.

Symptomatic hypertension often cannot be distinguished from hypertensive disease in its course. It may also be benign or malignant. This circumstance allows any form of arterial hypertension to be considered a diagnostic problem which can only be solved by a physician who is skilled in all clinical and auxiliary methods of examination to perfection. The curability of some types of symptomatic hypertension is sufficient ground for a more detailed account of the modern methods of their diagnosis.

Clinical Criteria in Differential Diagnosis of the Forms of Arterial Hypertension

In taking the medical history it is necessary to pay close attention to the symptoms and signs distinguishing the given case of the disease from the typical course of hypertensive disease described above. The cause of arterial hypertension may often be identified during interrogation of the patient. Particular attention should be focused on kidney diseases suffered in the past or the earlier existence of signs regularly found in such diseases.

Detailed questioning sometimes reveals that the patient had suffered puffiness of the face and hypertension long ago, or that protein and a large number of leucocytes had been found in the urine for several years. In such cases arterial hypertension may prove to be a consequence of glomerulonephritis or pyelonephritis that had not been recognized in good time.

Some diseases are encountered in one and the same family with particular consistency. Information volunteered by a patient with arterial hypertension that his relatives had polycystic renal disease, adrenal tumours or diabetes mellitus should be regarded as indirect evidence of the possible association of his hypertension with some congenital developmental anomaly of the kidneys or with some type of hereditary disease.

Arterial hypertension is most likely to be symptomatic if found

for the first time in a person under 20 or over 50 years of age. Special care must be taken to reveal the frequency of hypertensive crises. Frequently recurring hypertensive crises are characteristic of tumours of the adrenal medulla. The characteristic triad of paroxysmal hypertension (palpitation, profuse perspiration and headache) is encountered in approximately 50 per cent of patients with pheochromocytoma. Polyuria, nycturia and attacks of muscular weakness which seems to occur as if by chance, are mainly observed in tumours of the adrenal cortex.

Hypertension is most likely symptomatic if it had begun suddenly and immediately stabilized at high levels. As it is noted above, during the first years benign hypertensive disease is always marked by moderately increased arterial pressure and does not produce subjective sensations of illness.

The main purpose of physical examination also consists of attempts to find signs allowing symptomatic hypertension to be differentiated from essential hypertension. The severity of arterial hypertension is determined at the same time, and a program is planned of auxiliary laboratory tests the results of which will make it possible to identify the cause of arterial hypertension in the given patient.

Oedema of the face and trunk and especially periorbital oedema are usually evidence of the association of increased arterial pressure with affection of the kidneys. Oedema may also be encountered in hypertensive disease, but only if the latter is complicated by heart failure. Oedema in such cases of hypertensive disease develops on the lower limbs and lower trunk, as a rule. It differs from oedema of renal origin in colour, consistency and the condition of the overlying skin.

Raynaud's syndrome, persistent arthralgia, and polyarthritis are usually not encountered in hypertensive disease. They are commonly caused by collagenoses, gout, systemic vasculitis, cryoglobulinaemia and other gammapathies which are often marked by increase of arterial pressure. Hirsutism, a moonlike face and obesity of the trunk with the appearance of skin striae also allow hypertensive disease to be excluded and arterial hypertension to be related to the symptomatic forms. A tumour-like mass palpated in the abdominal cavity may prove to be a kidney affected with polycystic disease, which often induces an increase in arterial pressure. The higher the arterial pressure, the more easily is pulsation of the carotid, subclavian and radial arteries revealed. Pulsation of these arteries is drastically diminished in arterial hypertension caused by arteritis of the aorta and its branches or by coarctation of the aorta.

The differential diagnostic significance of abdominal murmurs is generally known. It has been convincingly demonstrated on a wealth of material that systolic murmur over the abdominal aorta

may be caused by stenosis of the renal artery and that arterial hypertension in these patients often proves to be symptomatic. Examination of the fundus oculi often helps in distinguishing hypertensive disease from arterial hypertension induced by diabetic glomerulosclerosis and brain tumours.

Auxiliary Examination Methods in Arterial Hypertension Diagnosis

It has recently come to light that the incidence of symptomatic hypertension is much higher than it had been assumed earlier when its diagnosis was established only from the results of the clinical methods of examination mentioned above. It is now much easier to clarify the causes of arterial hypertension by means of auxiliary investigations the volume of which is determined by the rule: better perform an extra examination than miss a potentially curable form of symptomatic hypertension.

The diagnosis of hypertensive disease can be established only in those cases of arterial hypertension in which all causes of the hypertensive syndrome listed in Supplement IV-1 have been excluded. The diagnosis of malignant hypertensive disease should be approached with particular caution. This disease was encountered much more frequently during World War II and in the first years after it than in our times. Its incidence in 1965 decreased by 95.5 per cent as compared to that in 1945. In the period between 1964 and 1968 the diagnosis of malignant hypertensive disease was made in only 0.1 per cent of patients with arterial hypertension treated at the Institute of Cardiology, AMS USSR (Ratner, 1972).

The figures cited provide grounds for the assumption that in our times malignant arterial hypertension is symptomatic as a rule. This cannot be said of benign hypertension, the causes of which both in the past and at present remain unknown. In appraising the statistical data cited above it should be borne in mind that they cannot influence the diagnosis in each case of hypertension but should provide incentive for the physician to re-examine the patient so as to rule out all its possible causes, very rare ones among others.

Renal Hypertension

Symptomatic hypertension, whether benign or malignant, is commonly of renal origin. Supplement IV-1 lists all kidney diseases that are marked by increased arterial pressure. Clinical experience

provides grounds for the belief that arterial hypertension appears only when the diseases listed had caused affection of the kidneys identifiable by modern methods of examination. The initial stages of these diseases are usually not attended by arterial hypertension. Consequently, if we speak of the renal origin of arterial hypertension then in each case we must disclose functional and morphological signs of marked affection of the kidneys.

Arterial hypertension of renal origin is most commonly consequent upon pyelonephritis or chronic glomerulonephritis. Both benign and malignant forms of hypertension may develop in these two diseases. The differential diagnosis with the corresponding forms of hypertensive disease is a difficult problem and often calls for many special methods of examination.

Chronic pyelonephritis is among the most commonly encountered kidney diseases in all age groups. According to Pytel (1972), arterial hypertension is found in approximately 3.2 per cent of patients with unilateral chronic pyelonephritis. Its true incidence exceeds this figure probably. Because of the poorness of the clinical symptoms, this pyelonephritic arterial hypertension is often mistaken for essential hypertension. Questioning the patient thoroughly about urological diseases among his relatives, about any urological diseases which he himself had suffered in the past and the diagnostic methods of examination to which he had been subjected because of them considerably reduces the number of such diagnostic errors.

Chronic pyelonephritis proves to be a particularly frequent cause of arterial hypertension in young women. Its exacerbation often takes an atypical course with short-term dysuria and is mistaken for a vaginal infection, e.g. defloration cystitis. Some authors link not only nephropathy of pregnancy but even any diminution of renal concentration function in pregnancy with asymptomatic infection of the urinary tract.

Asymptomatic infection of the urinary tract is encountered in 3 to 7 per cent of women in pregnancy. The prescription of antibiotics considerably improves the concentrating capacity of the kidneys sometimes. As far as we know, the diagnostic significance of this test has not been studied systematically.

Arterial hypertension is rarely the only sign of pyelonephritis. The increase in arterial pressure in many patients with this disease is accompanied by dysuric phenomena, thirst, polyuria, pain or unpleasant sensations in the lumbar region, increased fatiguability, and short-term elevation of body temperature. These phenomena may be explained by the inflammatory process in the kidneys, impaired flow of urine from the upper urinary tract, selective affection of the functions of the tubular epithelium, and the existence of latent or mildly pronounced renal insufficiency.

Arterial hypertension is usually only one of the components of

the constellation of symptoms and signs of pyelonephritis mentioned above. Increased arterial pressure in most cases of mild hypertensive disease (in contrast to that in pyelonephritis) is not only the principal, but the only sign of the malady. The existence of monosymptomatic pyelonephritis does not refute this differential-diagnostic principle because pyelonephritis producing only a single symptom, just like monosymptomatic glomerulonephritis, is a relatively rare occurrence and is encountered only in one of its developmental stages. Moreover, in many cases of arterial hypertension which seems at first to be monosymptomatic, we were able to disclose by purposeful interrogation a constellation of symptoms and signs characteristic of symptomatic hypertension.

The objective signs of chronic pyelonephritis in the early stages may noticeably and even sharply differ from those in the late stages. Bacteria, casts, leucocytes, a small amount of protein and sometimes red cells are found in the urine in the early stage of the disease. With the gradual advancement of the disease, the urinary syndrome becomes less pronounced. Haematuria and leucocyturia gradually disappear and in some cases only traces of protein are detected in the urine. Arterial hypertension becomes the principal syndrome of the disease, to which azotaemia and anaemia develop in attendance at a later stage.

In a definite stage of pyelonephritis development, arterial hypertension may be its principal and sometimes its only clinical syndrome. Such cases of chronic pyelonephritis are differentiated from hypertensive disease by the results of renography, kidney scanning, pyelography and examination of the urinary sediment.

Bacteria, though in a small number, are found in the urine of approximately 6 per cent of patients with malignant arterial hypertension like in the urine of healthy individuals. Bacteriuria precedes pyelonephritis and is a regular occurrence in its early stages. Pyelonephritis should be suspected when more than 100 000 bacteria are contained in 1 ml of urine collected with a catheter. The bacteria count is made by bacterioscopic, bacteriological and indirect methods.

The bacterioscopic method is only used for determining bacteriuria in freshly voided urine because it is difficult to prevent infection of stored urine or vigorous growth of bacteria already contained in it. The extent of bacteriuria is determined from the number of bacteria found either in the field of vision or in one or two squares of the counting chamber. Pyelonephritis may be suspected when more than two bacteria are visible in one large square. Urine cultures on solid media make it possible to appraise the extent of bacteriuria more precisely and to grow a pure culture of the causative agent and test its sensitivity to antibiotics. The possibility of solving diagnostic and therapeutic problems in a single examina-

tion is the main advantage of the bacteriological method.

Indirect methods for testing the intensity of bacteriuria by adding sulphanilic acid and alphanaphthylamine or triphenylytetrasole chloride to the urine are commonly used in practice. The precipitation of a red sediment indicates that 1 ml of the urine tested contains more than 100 000 microbial bodies. These tests are of small value in making the differential diagnosis. Their result is positive in almost 80 per cent of cases with pyelonephritis.

Much attention was directed at clarifying the differential diagnostic significance of the formed elements in the blood, namely, red cells, leukocytes and casts. The Kakovski-Addis method reveals up to two million red cells, up to four million leucocytes and up to 100 000 casts in the daily urine of patients with benign hypertension, just as in the daily urine of a healthy person. The number of leucocytes excreted with the urine is increased in pyelonephritis and bacterial infections of the urinary tract. The leukocyte count in the daily urine increases sharply in active pyelonephritis and noticeably exceeds the red cell count in typical cases. The content of casts remains unaltered.

The urine of patients suffering from pyelonephritis and other inflammatory diseases of the urinary tract often contains 'active' leucocytes differing from ordinary ('inactive') leukocytes by a characteristically mobile cytoplasm. In isosthenuria or hyposthenuria the active leucocytes in the urine swell drastically, doubling the normal size. An aqueous-alcohol mixture of safranine and gentian violet stains the cytoplasm of these large leucocytes pale blue. According to some authors, the pale leucocytes (Sternheimer-Mulbin cells) are found in approximately 40 per cent of cases with pyelonephritis attended by hypertension.

Attempts were made to increase the significance of urinary sediment examination in the diagnosis of pyelonephritis by simultaneously determining the number of 'active' and ordinary leucocytes in the urine and the ratio of the 'active' and 'inactive' leucocytes, and by conducting provocative tests. It is allowed that the prescription of some agents, e.g. prednisolone, leads to the exacerbation of pyelonephritis, as a result of which the number of leucocytes and bacteria in the urine increases and 'active' leucocytes often appear.

Many authors point to the immense diagnostic significance of provocative tests. It is believed that intravenous infusion of 40 mg of prednisolone is attended by the release of "active" leucocytes from the inflammatory focus in the kidneys into the urine. Our experience is comparatively of lesser scope than that of these authors, but it does not provide grounds for including the prednisolone test among tests capable of noticeably facilitating the differential diagnosis between pyelonephritis and benign hypertension.

The differential diagnostic importance of the various methods

for counting the formed elements in the urine and the results of provocative tests is often overestimated. The content of formed elements in the urinary sediment, just as the results of the provocative tests, in the different stages of pyelonephritis may prove to be dissimilar. Active leucocytes are often found in acute pyelonephritis. With the gradual advancement of the disease, proteinuria diminishes while the urinary sediment becomes more and more sparse. The Sternheimer-Malbin cells are found only in some cases of chronic pyelonephritis with the activity of the inflammatory process preserved to some measure. In pyelonephritic contracted kidney only traces of protein are sometimes found in the urine, which may be completely free of formed elements.

Hypertensive disease is most easily distinguished from symptomatic hypertension in pyelonephritis by comparing the functional state of the right and left kidneys. In involvement of both kidneys in the inflammatory process, one is affected more than the other as a rule. The function of one kidney is always impaired to a greater extent than that of the contralateral kidney. In hypertensive disease the function of both kidneys is disturbed to an equal extent as a rule. Isotope renography, infusion urography and scanning of the kidneys are among the reliable and safe methods of comparative appraisal of the functional state of the right and left kidneys.

Isotope renography is usually performed with ^{131}I-hippuran. The renograms of the right and left kidneys in patients with non-complicated essential hypertension (as in healthy persons) are symmetrical. Following intravenous injection of ^{131}I-hippuran, maximum radioactivity over the kidney in a healthy individual appears in three to four minutes. The period of hippuran half-life in blood is eight to ten minutes. The differences in time of maximum ascent of the renograms do not exceed 1 minute, while the differences in the value of the period of isotope half-life do not exceed 2 minutes.

In pyelonephritis the renograms of the right and left kidneys differ from each other in the height of ascent and the time of its appearance. The functional asymmetry of the kidneys is best demonstrated in the excretory phase of the renogram. The functional asymmetry of the kidneys in pyelonephritis and some of the peculiarities of their morphological structure may be revealed by scanning. The scanograms demonstrate a diminution in the size of the affected kidney, reduced and irregular accumulation of the isotope in it. The extent of vicarious hyperfunction of the healthy contralateral kidney may be simultaneously appraised. Kidney scanograms in benign hypertensive disease do not differ from the scanograms of a healthy kidney.

Comparative data on the functional state of the kidneys and upper urinary tract may be obtained by means of excretory urography which is advisable to be accomplished by the infusion meth-

od. In cases with benign hypertensive disease the contrasting of both kidneys begins and ends simultaneously. The principal sign of pyelonephritis (just as of other prevalently unilateral renal diseases) is asymmetric contrasting. The contrast medium appears later on the side of the affection or on the side of the kidney that is involved to a greater extent than on the healthy or less affected side. The concentration capacity of the affected kidney is also disturbed, which is judged by the time of the maximum contrasting. Delayed excretion of the radiocontrast medium from the kidney that is more affected is considered a particularly characteristic sign.

Impaired muscular tone of the urinary tract is displayed by spasms of the pyelocalyceal system and changes in the shape of the calyces and renal pelvis. With the advancement of the disease the spasmodic phase is replaced by the atonic phase as a result of which the calyces and pelvis are distended. The initial parts of the calyces become rounded, their necks constricted, while the edges become mushroom-shaped. Contraction of the affected kidney occurs in the late stages of the disease. It becomes smaller. The minor calyces come closer to each other. The structure of the pyelocalyceal system is best demonstrated on a retrograde pyelogram which is usually resorted to when the results of infusion renography are insufficiently clear.

Renal angiography discloses deformity of the arterial bed. As the result of irregular development of the cicatricial processes, the symmetry of renal artery branchings is disturbed. Because of the obliterated small cortical vessels, the angiographic pattern of pyelonephritic kidney acquires the characteristic appearance of a charred tree. Renal angiography is performed for distinguishing late stages of pyelonephritis from occlusive renal hypertension and hypoplasia of the kidney. The methods mentioned above allow a correct diagnosis to be made in approximately 80 per cent of cases with pyelonephritis.

The diagnosis of pyelonephritis as one of the causes of arterial hypertension noticeably improved after the introduction into clinical practice of needle biopsy of the kidneys. The focal character of the affection of the kidneys in pyelonephritis provided grounds for some authors to doubt the diagnostic value of this method. There is evidence that needle biopsy is of decisive significance in making the diagnosis in all doubtful cases of pyelonephritis.

Renal biopsy in pyelonephritis reveals interstitial sclerosis with atrophy of the tubules and lymphohistiocytic infiltrates, periglomerular sclerosis, deformity of the arteries with arteritis and perivascular sclerosis, and alternation of areas of markedly altered and almost normal renal tissue. In hypertensive disease, only hyalinosis of occasional glomeruli and altered small arteries and arterioles are found (Petrov, 1974).

Pyelonephritis may be a concomitant to other diseases of the kidneys. It particularly often complicates diabetes mellitus and obstructive uropathy developing due to functional disorders or structural anomalies of the urinary tract. Unilateral or bilateral obstructive uropathy is a regular occurrence in obstruction of the ureter with a stone, inflammatory strictures of the urethra and ureters, vesicoureteral reflux, compression of the urinary tract by tumours, cysts or cicatrizing connective tissue, and in other diseases listed in Supplement IV-1. Each of these diseases may lead to the development of pyelonephritis which becomes one of the causes of arterial hypertension.

Everyday clinical practice shows that the longer the history of urolithiasis, the more frequently it is combined with arterial hypertension. Most authors consider chronic calculous pyelonephritis to be the main cause of hypertension in patients with urolithiasis. The diagnosis of this form of symptomatic hypertension proves easy in most cases because of the sufficiently clearly outlined clinical picture of the principal disease.

Polycystic disease and other congenital anomalies of the kidneys. Polycystic disease of the kidneys is among the rarer renal diseases. It is found in 0.35 per cent of autopsies. Arterial hypertension is encountered in approximately half of the cases with this disease. It is caused either by pyelonephritis or ischaemia of the kidneys resulting from mechanical compression of the renal arteries by cysts or from obstruction to the flow of urine in the upper urinary tract. Hypertension in solitary renal cysts and hydatid disease of the kidneys is also attributed to these mechanisms.

Polycystic disease of the kidneys is often complicated by pyelonephritis and less frequently by suppuration of occasional cysts and the formation of stones in the kidneys. These complications are usually unilateral. The disease may be asymptomatic for a long time. The first complaints usually appear at the age of 35 to 45 years.

Arterial hypertension in polycystic disease of the kidneys is at first transitory and resembles benign hypertensive disease in its clinical course. The patient's working capacity is not impaired, but he often complains of dull pain in the lumbar region, usually on one side. Arterial hypertension of a continuous type develops later with changes in the fundus oculi and hypertrophy of the left heart ventricle. Recurrent renal haemorrhages are often met with.

Enlargement of the kidneys characteristic of this disease, frequently combined with enlargement of the liver, is often revealed by careful palpation of the abdominal organs and always by X-ray examination. Even mild abnormalities found by urinalysis must be accepted as an indication for more detailed examination of the anatomical and functional state of the kidney. In combination with

detailed and purposeful interrogation of the patient these small signs facilitate timely identification of the true cause of arterial hypertension. The development of arterial hypertension in some other congenital developmental kidney anomalies (duplication, agenesis, dystopy, hypoplasia, fusion of the poles) and in diseases of the ureters and lower urinary tract with impaired flow of urine is attributed to the occurrence of pyelonephritis. The true cause of hypertension in these conditions is identified in most cases by the urologist and not the internist.

Diabetic glomerulosclerosis. Arterial hypertension in diabetes mellitus is mostly consequent upon attendant intercapillary glomerulosclerosis (Kimmelstiel-Wilson's syndrome). The development of diabetic glomerulosclerosis is linked with metabolic disorders in diabetes, the manifestations of which grow with the duration and the severity of the principal disease. Proteinuria, inconstant and usually mild, is the first and sometimes the only sign of this complication of diabetes mellitus. Intermittent proteinuria may last 6 to 8 years. Arterial pressure during this period may remain normal or sometimes increases.

In the later stages of the disease, proteinuria becomes constant and oedema develops. The arterial pressure is often elevated in this stage of diabetic glomerulosclerosis. The clinical picture of the malady resembles that of the mixed form of chronic glomerulonephritis rather than hypertensive disease. Further development of glomerulosclerosis leads to a diabetic contracted kidney. High hypertension and chronic renal insufficiency appear.

Arterial hypertension in diabetic glomerulosclerosis usually appears for the first time at an elderly or old age and is often mistaken for hypertensive disease. In making the differential diagnosis between these diseases one should particularly bear in mind the following: (1) proteinuria in benign hypertensive disease, if encountered at all, occurs only during severe hypertensive crises and on the first one or two days after they cease. Proteinuria in diabetic glomerulosclerosis exists irrespective of the hypertensive crises; (2) glomerulosclerosis appears in the late stages of diabetes when most patients already have characteristic signs of diabetic microangiopathy which is particularly clearly pronounced in the retinal vessels. Such changes are never encountered in hypertensive disease; (3) arterial hypertension in a patient with diabetes may be consequent upon attendant pyelonephritis or stenosing atherosclerosis of the renal artery. Diabetic glomerulosclerosis is a diffuse disease. Both kidneys are equally involved. Pyelonephritis is unilateral in most cases. In bilateral pyelonephritis, one kidney is usually affected more than the other. Urological examination allows these forms to be distinguished from each other. Needle biopsy of the kidneys is recommended in cases presenting a diagnostic problem.

The diagnosis of renal arterial stenosis is made from the results of aortography.

Chronic glomerulonephritis. Acute onset of diffuse glomerulonephritis is an exception rather than a rule today. According to Petrov (1974), only 14.8 per cent of his patients recalled that they had suffered from acute nephritis in the past. In all the other cases chronic glomerulonephritis began insidiously. About 45 per cent of patients with chronic nephritis were placed under medical observation because of arterial hypertension.

In taking the medical history, it is important in every case with arterial hypertension to clarify whether or not it is linked with the urinary syndrome in timing. Proteinuria and microhaematuria may be revealed in patients with chronic glomerulonephritis long before the appearance of hypertension (at times years in advance). The urinary syndrome is never found in the initial period of hypertensive disease. Proteinuria and microhaematuria appear for the fist time only during a hypertensive crisis, i.e. usually several years after more or less stable hypertension develops.

Elevation of arterial pressure during pregnancy may be regarded as indirect evidence of nephritis or pyelonephritis suffered earlier, because these diseases are the most common causes of nephropathy in pregnancy. Such information, unfortunately, is disclosed in no more than one third of patients with chronic glomerulonephritis. It therefore proceeds that negative information in the medical history by no means rules out the possible association of arterial hypertension with chronic nephritis, whereas positive findings allow this association to be regarded as very probable.

Arterial hypertension in chronic nephritis, as in hypertensive disease, is transitory at first but becomes permanent later. The diastolic pressure usually does not exceed 110 mm Hg. Arterial hypertension is noticeably lower in the morning than in the evening. Despite the high arterial pressure, patients, the young in particular, fully retain their working capacity. Diminished function of the kidneys is sometimes disclosed only 15 to 20 years after the onset of arterial hypertension. The changes in arterial pressure in the hypertensive form of chronic glomerulonephritis before the appearance of signs of renal insufficiency may completely imitate its changes in benign hypertensive disease.

The compared diseases nonetheless differ in the severity of changes in the cardiac and cerebral vessels. Hypertrophy of the left ventricle and the clinical and electrocardiographic signs of coronary insufficiency are pronounced more sharply in hypertensive disease, as a rule, than in chronic glomerulonephritis. A similar pattern is seen in the changes in the fundus oculi. These differences in the severity of abnormalities in the heart and brain are usually attributed to the different height of arterial pressure and the different

extent of metabolic disorders. The changes in the fundus oculi are mainly determined by the height and duration of hypertension. Their less pronounced character in chronic glomerulonephritis is explained by the fact that in most cases of this disease the level of arterial pressure is lower.

Hypertensive disease is complicated by atherosclerosis with such regularity that Myasnikov even suggested distinguishing its stages according to the severity of atherosclerosis in the aorta and the large cerebral and cardiac vessels. The appearance and steady increase in the frequency and severity of attacks of angina pectoris and electrocardiographic signs of coronary insufficiency are just as typical of essential hypertension as the appearance and gradual growth of signs of renal insufficiency is typical of chronic nephritis. The detection of signs of atherosclerosis of the aorta and coronary arteries in benign arterial hypertension has long been regarded as a sign of hypertensive disease, while diminished rate of glomerular filtration as a sign of chronic glomerulonephritis.

The longer the time from the onset of the disease, the clearer are the differences in the character of the complications attending the compared diseases. Patients with benign hypertension usually die from a cerebral stroke, myocardial infarction or heart failure consequent upon postinfarction cardiosclerosis. Renal insufficiency usually does not develop in these patients. Chronic nephritis and particularly its hypertensive form are no absolute guarantee against myocardial infarction and stroke, but the longer the time elapsing from the onset of the disease, the more obvious is the threat of fatal renal insufficiency and its complications.

In the early period of hypertensive disease, symptoms of atherosclerosis of the aorta and coronaries are still not clearly defined and arterial hypertension is no different in its course from that in chronic glomerulonephritis. At the same time, the identification of the causes of arterial hypertension in such cases is of immense practical significance because the results of this study determine the volume and character of the curative and preventive measures. The detection of humoral or morphological signs of an autoimmune process in the body and the results of repeated urinalysis may be of considerable diagnostic value in such cases of recently developed hypertension.

The significance of the urinary syndrome in establishing the differential diagnosis depends on its severity and the constancy of its revelation in repeated examinations of the urine. Proteinuria of more than 1 g/24 hours may be regarded as indirect evidence of the association of arterial hypertension with a primary kidney affection. This assumption becomes all the more probable when erythrocyturia and leucocyturia are found simultaneously with proteinuria. Proteinuria and erythrocyturia are not encountered in mild

hypertensive disease. In severer cases of this disease the amount of protein in the daily urine still does not exceed 1 g.

The differential diagnostic importance of the urinary syndrome also depends on the regular examination of the urine. A small amount of protein and occasional red cells are found in benign hypertensive disease only in the first one or two days after a crisis. Exacerbations of chronic nephritis are marked by more or less long periods of proteinuria and microhaematuria.

Still another peculiarity of the urinary syndrome in chronic glomerulonephritis must be borne in mind. Proteinuria is believed to be a characteristic symptom of this disease, but in 15 to 20 per cent of cases with the hypertensive form of chronic glomerulonephritis, examination of the urine shows normal values from time to time. As it is pointed out above, chronic pyelonephritis may also be marked by a sterile urine and no abnormalities in its sediment. These diseases may be differentiated in many instances by determining the leucocyte and red cell counts in the urine. Chronic glomerulonephritis attended by a mild urinary syndrome is nevertheless characterized by higher excretion of red cells in the urine than is encountered in health. The red cell count in the urine of a patient with chronic glomerulonephritis is higher than the leucocyte count. The red cell count in the urine of a patient with chronic pyelonephritis is lower than the leucocyte count. Renal biopsy in such cases which are a diagnostic problem is the most reliable method for distinguishing chronic glomerulonephritis from pyelonephritis and from hypertensive disease. Changes are found in the walls of the small renal arteries and arterioles in hypertensive disease. The changes in the kidneys in chronic glomerulonephritis are marked by great variety. Morphological signs of nephritis are disclosed in the glomeruli, tubules, vessels and connective tissue. Immunomorphological study of the bioptic material reveals deposition of immunoglobulins in the mesangium and walls of the tubular capillaries in chronic glomerulonephritis.

The results of needle biopsy are of tremendous value in making the diagnosis. This method, unfortunately, cannot be applied in every instance of arterial hypertension when the diagnosis is still enigmatic, because of the difficulties in obtaining the renal tissue and because of possible complications.

The diagnosis may only be made from bioptic material containing at least five or six renal glomeruli. Transcutaneous biopsy provides material of such volume in approximately 80 per cent of cases. The more severe the sclerotic changes in the organ, the less frequently renal tissue can be collected by biopsy.

Each renal biopsy is attended by microhaematuria of several days. Macrohaematuria is a much rarer occurrence. Retroperitoneal haematoma is the most serious complication; its growth in

two cases known to us called for surgery. The performance of needle biopsy of the kidneys is attended by a certain degree of risk. It is resorted to only in cases when it proves impossible to establish the diagnosis by other methods.

Hypertensive disease, chronic glomerulonephritis and pyelonephritis are the most common causes of arterial hypertension with no abnormalities in the urine or with a mild urinary syndrome. The methods for separate appraisal of the functional state of the right and left kidneys described above reveal in most cases objective diagnostic criteria distinguishing pyelonephritis from chronic glomerulonephritis. This may be aided to some extent by giving due consideration to the peculiarities of the course taken by both diseases. Signs of the nephrotic syndrome, even if mild, should always be accepted as a weighty argument in favour of chronic glomerulonephritis. Any indications of short-term oedema in the past are just as important in differential diagnosis as oedema found when the patient is examined. The urine protein content in pyelonephritis rarely exceeds 1-2 g/l. A more intensive proteinuria, other conditions being equal, should be regarded as evidence in favour of chronic glomerulonephritis. Malignant hypertensive disease is distinguished from chronic glomerulonephritis and pyelonephritis by the course of chronic renal insufficiency developing in the terminal stages of these diseases.

Vascular Forms of Hypertension

Renovascular hypertension. Stenosing lesions of the large aortic branches are sometimes attended by arterial hypertension. When the renal arteries are affected, the condition is called renovascular hypertension. Affection of the branches of the aortic arch is sometimes attended by moderate hypertension which Maxwell (1970) calls centrigenic thus linking its development with ischaemia of the vasomotor centre. Definite importance in the mechanisms of the development of this hypertension is also attributed to impaired function of the baroreceptors of the carotid-aortic reflexogenic zone.

Renovascular hypertension accounts for 2.2 per cent of all cases with arterial hypertension. According to the clinical course, it may be either malignant or benign. Knyazeva (1974) encountered malignant renovascular hypertension in 34 (29 per cent) of 117 patients. The great variety of the clinical manifestations and the absence of pathognomonic signs makes the diagnosis of this form of arterial hypertension difficult. This diagnosis should be suspected in all cases in which questioning of the patient discloses clinical features which are not typical of benign hypertensive disease.

As it has been pointed out above, arterial pressure in hyperten-

sive disease usually becomes stably increased after the age of 30-35 years. The appearance of stable hypertension before this age is characteristic of the symptomatic hypertension, a common form of which is renovascular hypertension.

Hypertensive disease in the elderly (in persons above 60 years of age) is usually benign. Hypertensive crises become less frequent and less severe. Signs of atherosclerosis of the aorta and the cerebral and coronary arteries gradually come to the forefront. If arterial hypertension develops for the first time at an elderly age, its association with affection of the renal arteries should be considered before all else. This assumption seems all the more possible the higher the diastolic pressure and the more pronounced the changes in the fundus oculi.

Vascular forms of hypertension are often combined with long-term, usually moderate fever, leucocytosis, and increased erythrocytic sedimentation rate. Their characteristic symptoms are as follows: asymmetry of arterial pressure in the limbs, absence of the pulse or a clear-cut diminution of its amplitude on the upper or lower limbs, dizziness and syncope. Vascular murmurs, e.g. a long murmur over the abdominal aorta, are encountered in rare cases in these forms of hypertension.

These characteristic features are, unfortunately, not found in every case of vascular hypertension, but their disclosure indicates the need to appraise the anatomical condition of the aorta and its branches objectively. Aortography is the only method for objective diagnosis of vascular hypertension. Isotope renography, kidney scanning, and excretory urography described above are applied as methods for preliminary examination. They demonstrate the functional condition of each kidney separately.

In unilateral stenosis of the renal artery, the kidney on the affected side proves to be smaller than the contralateral unaffected kidney. The difference in their length usually exceeds 1 cm. In addition, the healthy kidney is contrasted and freed of the contrast medium earlier than the kidney with stenosis of the artery supplying it.

Cases with renovascular hypertension were described in which the results of ^{131}I-hippurane isotope renography and excretory urography revealed no differences in the function of both kidneys. The insufficient diagnostic value of these methods is explained either by adequate development of the collaterals on the side of the affected renal artery, or by the short duration of the disease which as yet had not resulted in diminished function of the kidney on this side.

Many authors emphasize the high diagnostic value of increased plasma renin activity in patients with renovascular hypertension. The factual material accumulated to date shows that the renin concentration increases in malignant hypertension of any origin. Moderate renal arterial stenosis may be marked by the benign hyperten-

sive syndrome. The renin concentration in the blood of these patients remains normal (Kirkendall and Overturf, 1973).

Vascular hypertension is most commonly a consequence of atherosclerosis of the renal arteries, their fibromuscular hyperplasia and arteritis of the aorta and its branches. Arterial pressure in systemic circulation increases in all cases when the lumen of the renal artery is constricted by more than half.

Atherosclerosis of the renal artery. Atherosclerotic stenosis of the renal artery is mainly encountered in males of middle and elderly age. The stenosis is unilateral as a rule and localized at the orifice and in the middle part of the affected artery. Signs of atherosclerosis of the abdominal aorta are found at the same time, which are demonstrated on the angiograms as irregularities of its outline. Collateral circulation on the affected side is only slightly demonstrated. Nephrograms show diminished size of the kidney receiving blood from the constricted artery. Arterial hypertension consequent upon atherosclerosis of the renal artery is often malignant.

The diagnosis of this type of vascular hypertension is facilitated by the demonstration of signs of stenosing atherosclerosis in other vascular areas. A particularly scrupulous examination is necessary in revealing the syndrome of intermittent claudication developing as the result of atherosclerosis of the lower limb artery or bifurcation of the aorta, the carotid artery syndrome, and the subclavian-vertebral and other syndromes caused by lesions of the branches of the aortic arch. The results of the joint examination of the patients by an ophthalmologist and neurologist are important in revealing these syndromes.

Fibromuscular stenosis of the renal arteries is encountered in females under the age of 40 as a rule. The affection is unilateral in most cases. Several constricted segments, each followed by a poststenotic dilatation are found in the wall of the affected artery. Such an artery has the appearance of a string of beads.

The diagnostic symptoms of arterial hypertension of fibromuscular origin are as follows: the patient's age and sex, alternation of areas of stenosis and dilatation on the renal artery angiogram, localization of the stenosis in the middle third of the affected artery and not in its orifice, absence of pronounced collaterals on the affected side, and normal appearance of the aorta. Arterial hypertension in fibromuscular renal arterial stenosis may be benign or malignant.

Developmental anomalies of the renal arteries. Arterial hypertension caused by developmental anomalies of the renal arteries is a rare occurrence. Its diagnosis may be made only from the findings of aortography. Hypoplasia or aplasia of one of the renal arteries is found on the aortograms. Arterial hypertension incident to aneurysm of the renal artery is just as rare. Signs pointing to the possible association of arterial hypertension with a lesion of the renal artery

are as follows: high and usually stable hypertension at young age, a long murmur over the abdominal aorta (in the epigastrium or periumbilical region), a decrease in the size or disorders of the function of one of the kidneys.

The angiogram demonstrates a normal abdominal aorta which gives rise to the main renal arteries at the usual level. One of them has a diminished diameter, but regular contours. The kidney on the side of the hypoplastic artery is smaller than normal, while the contralateral kidney is hypertrophied. Contrasting of the kidney on the side of the lesion is delayed. In aneurysm of the renal artery, which may be congenital or acquired, the angiogram demonstrates a characteristic localized dilatation.

Arteritis of the aorta and its branches. Arteritis of the aortic branches is usually combined with aortitis which is localized in the arch of the aorta in some cases and in its abdominal part in others. Affection of the aorta along its entire length is sometimes encountered. The disease predominates among young females. The development of arterial hypertension in this disease is facilitated by stenosis of the renal artery, affection of the carotid-aortic zone and deficient blood supply to the vasomotor centre.

The clinical picture of the disease comprises a combination of general (non-specific) and local (vascular) symptoms and signs. The non-specific symptoms and signs include: general weakness, subfebrile temperature of long duration, moderate leucocytosis, increased ESR, changes in the plasma-protein composition, and the appearance of antibodies showing the existence of an autoimmune process.

The local signs of the disease develop gradually because of disturbance of the normal flow of blood in the aorta and its branches. Stenosis of the arteries is attended by continuous vascular murmurs which are often heard over the carotid, subclavian and femoral arteries and over areas of the anterior abdominal wall and lumbar region corresponding to the site of the abdominal aorta and its branches. Depending on the degree of the stenosis, the pulse on the limbs may be weak or not felt at all. It is precisely this sign that served as the grounds for designating occlusive lesion of the branches of the aortic arch 'pulseless disease'.

The asymmetry of arterial pressure in the limbs that is characteristic of this disease is caused by the unequal degree of stenosis of different branches of the aortic arch. Patients were encountered with increased arterial pressure only on one upper limb and even only on the lower limbs. The aortic branches are gradually stenosed with attendant development of collateral circulation.

Stenosis, and sometimes also occlusion of different branches of the aortic arch, gradually lead to deficiency of blood supply to the brain with syndromes typical of this condition, namely, the syndromes of the innominate and carotid arteries, the subclavian-verte-

bral and other syndromes, which are manifested by impaired function of the visual and auditory analysers, dizziness, syncope, and attacks of convulsions.

Extension of the inflammatory process to the abdominal aorta and renal arteries usually results in the development of arterial hypertension which often takes a malignant course. In two thirds of cases, stenosis of the renal artery is bilateral.

The characteristic angiographic signs of aortitis with affection of the renal artery are as follows: bilateral affection beginning at the orifices of the renal arteries and spreading approximately to their middle part, signs of renal arterial occlusion, adequate development of collaterals around the stenosed arteries, irregular outlines of the aorta and signs of stenosis of other branches of the thoracic and abdominal aorta. The diagnosis is verified by the identification of general (non-specific) and local (vascular) symptoms of the disease that are mentioned above.

The narrowing of the renal artery by an atherosclerotic plaque or an inflammatory infiltrate may lead to its occlusion the diagnosis of which may be made only from an angiogram. Sudden arrest of the contrast medium at the beginning of the main renal artery or along its length is the most characteristic sign of occlusion. The network of collateral vessels is demonstrated well only when the occlusion develops slowly. The patient's age and the character of the morbid process which had led to obstruction of the artery are also important. The collaterals have no time to develop in traumatic occlusion but are usually adequately developed in renal arteritis. The margins of the aorta in its atherosclerosis and aortitis are irregular; in traumatic occlusion of the renal artery, the aortogram is normal.

If the patient survives the acute period of renal arterial thrombosis, he develops occlusion hypertension. Torsion of the renal vascular pedicle and compression of the renal artery by a tumour or the crus of the diaphragm lead to the same result. If the contralateral kidney is normal, removal of the stenosis results in disappearance of hypertension.

Coarctation of the aorta is mostly localized proximal or distal to the site where the ductus arteriosus enters it. A constriction localized proximally to this duct often extends along the left subclavian artery, sometimes with involvement of its orifice. Coarctation localized distal to the ductus arteriosus is usually restricted in length. Blood is supplied to the lower part of the trunk from the collaterals developing mainly between the beds of the internal thoracic, subclavian and superior intercostal arteries arising above the site of constriction and the beds of the femoral and inferior intercostal arteries. In rare cases the aorta is constricted at the level of the diaphragm or in the abdominal segment. The diagnosis of constriction

of the ascending aorta is described in the chapter 'Cardiac Murmurs' (aortic supravalvular stenosis).

Coarctation of the aorta, particularly if it is distal to the ductus arteriosus, often causes no subjective disorders in childhood. Physicians examining children suffering from this disease usually diagnose a congenital heart disease. Later, when arterial pressure is measured for some reason or other, the diagnosis of hypertensive disease is made. Arterial pressure begins rising after the age of ten and by the age of 20-30 years it sometimes reaches 220/120 mm Hg. Most patients die before the age of fifty. The most common causes of death are heart failure (26 per cent), bacterial endocarditis (25 per cent), rupture of the aorta (21 per cent) and cerebral haemorrhage (12 per cent).

Non-complicated coarctation of the aorta in childhood is usually asymptomatic; complaints of headache and malaise are, in most cases, caused by the development of complications. The formation of a post-stenotic aneurysm is attended by subfebrile temperature and pain in the region of the heart and between the shoulder blades. General weakness and fever are encountered when the disease is complicated by bacterial endocarditis; severe headache from physical exertion occurs when arterial hypertension develops.

Timely operation results in full recovery of the patient. In examination of any patient with arterial hypertension it is therefore necessary to focus special attention on symptoms always found in coarctation of the aorta. Among these signs are: the patient's general appearance, intensified pulsation of the carotids and sometimes also of the aortic arch, a slow and weak pulse in the femoral artery and arterial pulsation at unusual sites (Vinogradov, 1951).

All patients with coarctation of the aorta have a characteristic appearance. The well developed muscles of the shoulder girdle and upper limbs are in contrast to the weakly developed muscles of the lower limbs. Deficient development of the gastrocnemius muscles is particularly striking. Regular palpation of the vessels provides information allowing the correct diagnosis to be made even before instrumental examination. Strong pulsation in the dilated and elongated aorta is always felt in the retrosternal fossa. The carotids are enlarged and their pulsation is often clearly visible on inspection of the patient. The pulse in the radial artery is tense and of a large amplitude. When the process extends to the orifice of the left subclavian artery, the pulse in the left radial artery is small while in the right radial artery it is strong; arterial pressure is high in the right hand but reduced or normal in the left. The pulse in the femoral artery is always much smaller than that in the radial artery. Moreover, the pulse in the femoral artery always appears earlier than the pulse in the radial artery in a healthy person but it always appears later than the pulse in the radial artery in a patient with

coarctation of the aorta. The pulse in the dorsal artery of the foot and the posterior tibial artery cannot be felt.

In coarctation of the aorta, arterial pressure is increased only in the arteries of the upper limbs. Its level is inconstant. Short-term elevations of arterial pressure occur from time to time and are usually mistaken for hypertensive crises.

Hypertension in the vessels of the upper girdle is one of the most constant symptoms of coarctation of the aorta. The level of arterial pressure in the upper limb vessels does not exceed normal values only in rare cases. Low pressure in the lower limbs with simultaneous hypertension in the vessels of the upper girdle is a sign verifying the diagnosis of coarctation of the aorta.

In coarctation of the aorta most organs are supplied with blood from collaterals which are developed to such an extent that they are obvious on first sight. The size of some collaterals differs noticeably with each patient and evidently depends on the individual variations in the structure of the vascular bed.

The development of the main anastomoses between the branches of the subclavian artery and the intercostal arteries leads to the appearance of subcutaneous arterial pulsation in unusual places, for instance, along the length of the ascending cervical artery and the lateral thoracic artery. Intensified pulsation in the intercostal arteries is often palpated and even visible. Visible pulsation in the first-fourth intercostal space close to the sternum often appears when the main anastomosis forms between the internal thoracic and inferior epigastric arteries.

Signs of collateral circulation are also detected in X-ray examination. The radiographs demonstrate characteristic notching of the lower costal margin, more clearly defined in the posterior parts of the ribs where, as is known, the intercostal arteries come in direct contact with the ribs. Notching of the lower margin of the ribs is a very valuable diagnostic sign of coarctation of the aorta; however, it is encountered only in powerful development of collateral circulation.

Among the valuable but inconstant diagnostic X-ray signs of coarctation of the aorta are the absence of the aortic projection on antero-posterior roentgenoscopy of the patient, narrowing of the shadow of the aorta where its descending part begins, and the 'clear field' in the retrocardial space.

A continuous murmur is one of the main signs of constriction of the isthmus of the aorta. The mechanism of the development of this murmur is evidently similar to that of systolic murmur in stenosis of the aorta due to a valvular defect; only the narrowing of the aorta is localized more distally. The murmur is usually heard in the precardiac region, on the neck, and often in the interscapular space at the level of the first to third thoracic vertebrae. It is general know-

ledge that systolic murmurs occurring in valvular heart diseases are not transmitted to the interscapular space, as a rule. Mirolyubov (1922) contends that a clinician who finds a murmur between the shoulder blades should bear congenital narrowing of the aorta in mind. In making the diagnosis the greatest importance should be attached not simply to the detection of a continuous murmur in the interscapular space, but to its simultaneous existence with a similar continuous murmur in the precardiac area. At the same time, one must not forget that the absence of a continuous murmur in the interscapular space does not rule out the diagnosis of coarctation of the aorta.

In most cases, the continuous murmur is best heard over the base of the heart, namely, in the second, sometimes in the third, intercostal space to the right of the sternum. Its intensity varies from moderate to very loud. In the latter case it is often attended by tremor. A continuous precardiac murmur is sometimes preserved in total atresia of the isthmus of the aorta also, although some authors claim that it should be absent in such cases.

It is well known that distal to the site of its constriction, the aorta is filled with blood from the intercostal arteries. In the places where these arteries enter the aorta, conditions are created for the appearance of the murmur which are similar to those occurring in the sudden flow of fluid from the narrow part of an elastic tube into a wider part. Consequently, the site of the narrowing of the aorta is not the only place where the murmur characteristic of the disease develops. In the light of what has been said it can be understood why the characteristic murmur may sometimes be most intensive on the anterior surface of the chest over the segments of the descending aorta, and not over the site of its constriction: we observed this phenomenon in a number of cases.

A sharp precardiac systolic murmur is heard in a patient with hypertensive disease only in severe atherosclerosis of the aorta and marked atherosclerotic cardiosclerosis. This occurs in elderly patients, as a rule; the working capacity is diminished. The physical endurance of patients in the initial period of coarctation of the aorta may not differ from that of healthy individuals. One of our patients was a member of a football team for many years. Resting briefly after a football match he could still play volleyball the same day or take part in training competitions of swimmers. A sharp vascular murmur and arterial hypertension in such patients proved to be compatible with good physical endurance, which is not characteristic of patients suffering from hypertensive disease combined with atherosclerosis of the aorta or atherosclerotic cardiosclerosis.

The main criteria for distinguishing coarctation of the aorta from hypertensive disease are as follows: early appearance of arterial hypertension; extraordinary development of collateral circulation;

dissociation between the height of arterial pressure in the vessels of the upper and lower limbs; a continuous murmur heard simultaneously in the precordium and at the back between the shoulder blades; a diminished and delayed pulse wave in the femoral arteries. Aortography is usually performed only for determining the exact site and length of the coarctation.

Periarteritis nodosa. Arterial hypertension in periarteritis nodosa is caused by specific affection of the renal artery sometimes combined with glomerulonephritis. Depending on the time when the renal vessels are involved in the inflammatory process, arterial hypertension develops either at the beginning of the disease or at later stages. The diagnosis is difficult only when arterial hypertension develops before the other signs of the principal disease or when symptoms of heart failure develop in a patient who is suffering from high arterial hypertension. The urinary syndrome in such cases is considered (depending on its severity) to be either a consequence of heart failure or a manifestation of malignant hypertensive disease.

Periarteritis nodosa begins in some cases as arterial hypertension of unclear origin which is mistaken for hypertensive disease. The true cause of this hypertension becomes clear several months later when fever, leucocytosis, proteinuria and numerous signs of involvement of other organs and systems appear. The cause of arterial hypertension which sometimes precedes the typical clinical picture of periarteritis nodosa by five or six years is still an enigma. Detailed examination and scrupulous dispensary follow-up of the disease manifestations during these five to six years disclose whether this hypertension develops 'essentially' or is a consequence of latent renal arteritis.

Diagnostic difficulties sometimes occur in the later stages of periarteritis nodosa too, when as a result of the spread of the process to the coronaries, attacks of paroxysmal dyspnoea appear first and are later followed by signs of right-ventricular failure with hepatomegaly and oedema of the subcutaneous tissue. The similarity with malignant hypertensive disease becomes still closer with the appearance of severe neuroretinopathy and a marked urinary syndrome.

Differential diagnosis is made easier because the syndromes listed are usually combined in the clinical picture of periarteritis nodosa with other syndromes which are not typical of malignant hypertensive disease. Such are fever, polyneuromyositis, neuritis, polyarthralgia, leucocytosis, increased ESR, and abdominal pain. The compared diseases also differ in their course. In malignant hypertensive disease arterial hypertension always precedes heart failure. The attacks of paroxysmal dyspnoea in such cases are always the consequence of left-ventricular insufficiency with characteristic pulmonary congestion. Body temperature remains normal. Paroxysmal

dyspnoea in periarteritis nodosa usually occurs in protracted fever caused by the principal disease.

Endocrine Forms of Hypertension

Conn's syndrome (primary hyperaldosteronism). Ever more attention has recently been attracted to hypertension induced by abnormally high activity of mineralocorticoids in the body (see Supplement IV-1). Conn's syndrome is a classical example of this type of pathological condition. Its clinical manifestations comprise arterial hypertension combined with increased aldosterone secretion resulting in the development of hypokaliaemia with characteristic nephropathy and muscle weakness.

The disease sets in with mild and brief elevations of arterial pressure and is mistaken, as a rule, for benign hypertension. The blood potassium content remains normal for a long time, which provided grounds for some authors to distinguish a special normokaliaemic stage of primary aldosteronism. In later stages of the disease hypokaliaemia develops while arterial hypertension takes a malignant course in about one fourth of the cases.

It was established that among 284 cases with primary aldosteronism adenoma was the cause of the disease in 84.5 per cent, diffuse or micronodal hyperplasia in 11.3 per cent, and adrenal carcinoma in 2.1 per cent of cases. In 2.1 per cent of patients operated on for Conn's syndrome, the adrenals proved to be normal. In 90 per cent of cases the adenoma was localized in the left adrenal, in 10 per cent of cases adenomas were bilateral or multiple.

The severity of aldosteronism is not determined by the size of the adenoma, which is sometimes so small that it is found with difficulty during the operation.

The content of aldosterone in blood and the excretion of its metabolites in the urine are increased in most, but not in all cases of Conn's syndrome. It is possible that aldosterone secretion in adenoma of the adrenal cortex (like the secretion of catecholamines in pheochromocytoma) intensifies and slows down periodically. It precedes from this that the diagnosis of Conn's syndrome should only be made from the results of repeated tests for the blood aldosterone concentration. In establishing the diagnosis, it is necessary to bear in mind the age fluctuations in the concentration of aldosterone in blood. In elderly and old age it is approximately half that in young individuals.

In typical cases, Conn's syndrome is marked by reduced renin activity in blood. This is explained by the inhibiting effect of aldosterone on the function of the renal juxtaglomerular apparatus. The blood renin content remains reduced even after the prescription

of a low-sodium diet and diuretics. It also remains low in pregnancy. These signs are widely used for distinguishing Conn's syndrome from hypertensive disease and arterial hypertension incident to renal arterial stenosis which have similar clinical manifestations.

The blood potassium content remains normal in the initial stages of Conn's syndrome, but hypokaliaemia develops later from time to time. In severe cases of the disease, marked hypertension is combined with permanent hypokaliaemia and metabolic alkalosis. Polyuria, which is encountered in 72 per cent of cases and is most intensive at night, and weakening of muscles, particularly those of the neck and proximal parts of the limbs, are a consequence of hypokaliaemia. The antidiuretic hormone has no effect on the severity of polyuria evidently because of the development of hypokaliaemic nephropathy. In rare cases, muscle weakness is complicated by temporary pareses and even by paralyses.

Patients with Conn's syndrome occasionally develop oedema which, like the other signs of the disease, disappears soon after removal of the adenoma.

To distinguish symptomatic hypertension in primary aldosteronism from hypertensive disease it is necessary to pay attention when collecting the medical history to the degree to which the symptoms and signs of hypokaliaemic alkalosis are pronounced. In the clinical picture it is most vividly seen in functional disorders of the kidneys and striated muscles. As it was stated above, hypokaliaemic nephropathy leads to the development of thirst and polyuria which are particularly intensive at night. Muscle weakness is at first perceived by patients as rapid fatiguability, tiredness. Inconstancy of muscle weakness is characteristic. It always occurs in attacks during which the patient cannot raise his hand or hold a glass, plate or other objects which had not seemed at all heavy before. Sometimes he finds it difficult to speak or raise his head.

Medication with aldosterone antagonists results in the disappearance of hypokaliaemic alkalosis. Aldactone or verospiron is prescribed in a daily dose of 300 to 400 mg for two to four weeks. Prior to and during the test the content of total and metabolizable potassium in the body is repeatedly determined. Arterial hypertension usually disappears at the same time as hypokaliaemic alkalosis, and renin and angiotensin appear in the patient's blood (Brown et al., 1972). When therapy is delayed, arterial pressure remains increased which is explained by the development of renal arteriolosclerosis. Arterial pressure in such cases stays increased after removal of the tumour.

Conn's syndrome should be suspected in all cases in which hypertension is combined with polyuria and muscle weakness or with rapidly decreasing physical endurance. In considering the differential diagnosis between Conn's syndrome and hypertensive disease,

it should be weighed that increased aldosterone content in blood and increased excretion of the products of its metabolism in the urine are encountered in all cases with Conn's syndrome at the onset and that the blood renin activity is either not demonstrated at all or is drastically decreased. It also proves to be reduced in 10 to 20 per cent of patients with hypertensive disease, but the aldosterone content in such cases is normal. Low blood renin activity combined with hyperaldosteronaemia is encountered both in Conn's syndrome and in arterial hypertension which is easily cured with dexamethasone.

Arterial hypertension incident to adrenal adenoma often disappears after treatment with aldosterone antagonists. The results of this trial therapy not only confirm the causal relationship of hypertension with increased aldosterone activity, but allow the effect of the operation on hypertension to be predicted. Hydrochlorothiazide therapy in such instances (a daily dose of no less 100 mg prescribed for four weeks) proves unsuccessful and results only in a sharp intensification of hypokaliaemia. In benign hypertensive disease, treatment with hydrochlorothiazide usually causes long-term and marked reduction of arterial pressure. Hypokaliaemia usually does not develop. A rapidly advancing course distinguishes malignant hypertensive disease from malignant hypertensive syndrome in primary aldosteronism.

Adrenal adenocarcinoma. Adenoma of the adrenal cortex is only one of the causes of Conn's syndrome. Its other causes are adenocarcinoma and hyperplasia of the adrenal cortex. Carcinoma, like adenoma, affects only one of the adrenals in most cases. The growth of the malignant tumour is attended by fever which is usually of an irregular type, abdominal pain, and microhaematuria. Loss of appetite leads to loss of body weight. Metastases, usually to the bones and lungs, appear in the late stages of the disease.

The results of X-ray examination are of decisive importance. By the time that arterial hypertension develops, the carcinoma is usually much larger than an adenoma. Displacement of the affected kidney is demonstrated on the infusion urograms or nephrograms. Deformity of the pyelocalyceal system is discovered on retrograde pyelograms. Pneumoren combined with tomography produces a clear image of the kidneys and adrenals and makes it possible to locate the tumour and determine its size.

Adrenal adenoma is characterized by increased aldosterone excretion in the urine; in adrenal carcinoma not only the content of aldosterone and its metabolites, but that of other corticosteroids are increased in the urine.

Hypersecretion of other mineralocorticoids. Hypertension incident to increased secretion of other mineralocorticoids closely resembles arterial hypertension caused by aldosterone hypersecretion

These mineralocorticoids have a less marked effect on sodium and potassium metabolism but are nonetheless capable of causing not only an increase in arterial pressure but hypokaliaemia too. Arterial hypertension caused by hypersecretion of deoxycorticosterone or its precursors is more known than the other forms. Brown et al. (1972) and other authors described isolated hypersecretion of 18-hydroxy-deoxycorticosterone and 11-deoxycorticosterone which was marked by arterial hypertension, inhibited blood renin activity, and pronounced hypokaliaemia. The amount of metabolizable sodium was increased, while the content of aldosterone and 11-hydroxycorticosterone in the blood was normal.

According to Brown et al. (1972), blood renin activity is reduced in approximately 25 per cent of patients with benign essential hypertension. The normal content of aldosterone and deoxycorticosterone provides grounds to consider that both hypertension and inhibited renin secretion in these patients are caused by the activity of mineralocorticoids which have still not been identified. This assumption is confirmed by the results of trial spironolactone therapy. The prescription of aldoctone or verospiron for these patients results in reduction of arterial pressure as in patients with primary aldosteronism.

It does not proceed from the abovestated, however, that all cases of arterial hypertension with reduced renin activity are consequent upon mineralocorticoid hypersecretion. Spironolactones are effective in many but far from all cases of hypertensive disease with diminished renin activity. Hypersecretion of mineralocorticoids is probably the cause of only one and not of all forms of essential hypertension.

Hypertension induced by primary hypersecretion of unidentified mineralocorticoids may be benign or malignant in its clinical course. The clinical picture at the onset may be no different from that of hypertensive disease. Favourable results of trial treatment with spironolactones in the dose mentioned above indicate that it is of symptomatic origin. The extensive use of spironolactones for diagnostic purposes enables this type of hypertension to be suspected long before its late clinical syndromes appear (hypokaliaemic nephropathy, hypokaliaemic pareses and paralyses). The final diagnosis is established from the content of mineralocorticoids in the blood or in the urine, from the diminution or complete disappearance of renin activity, and from negative results of urological examination.

Glucocorticoid hypersecretion. The *Itsenko-Cushing's syndrome* is encountered in many diseases. An iatrogenic Itsenko-Cushing's syndrome developing under the effect of corticoid therapy is now more common. Increased arterial pressure is found in 85 per cent of patients with this syndrome. The retention of sodium is sometimes

attended by mild oedema and decrease of renin activity. The patient's characteristic appearance, changes in the skin and neuropsychic sphere, and the symptoms of diabetes mellitus and osteoporosis make the differentiation of hypertension in the Itsenko-Cushing's syndrome from hypertensive disease easy. Arterial hypertension in some cases of the *Shereshevsky-Turner syndrome* is also attributed to congenital anomalies of corticosteroid synthesis.

Renin hypersecretion. Renin is one of the renal pressor factors. Its effect on the vascular tone is not caused directly but via angiotensin. The rate of renin secretion by the cells of the juxtaglomerular apparatus is controlled by nerve influences, the degree of stimulation of the mechanoreceptors of the renal arterioles and the sodium content in the distal tubule of the nephron. Marked renal ischaemia, irrespective of its cause, leads to increased renin secretion.

The secretion of renin increases noticeably during hypertensive crises and in malignant hypertension of any origin. It is believed that in all such cases ischaemia of one or both kidneys induces a rise in renin secretion by triggering one of the mechanisms described above. As a consequence, the activity of angiotensin II is augmented as a result of which spasm of the renal vessels is intensified still more and the rate of aldosterone secretion increases. If this vicious circle is not disrupted by the renal depressor factors, stable hypertension sets in, the characteristic sign of which is increased aldosterone excretion in the urine in intensified blood renin activity.

The clinical features of this type of arterial hypertension were studied in detail by Ratner et al. (1968) who established that high renin activity in malignant renovascular hypertension diminishes drastically after a successful operation, and that its diminution is always attended by normalization of arterial pressure and a decrease in the excretion of aldosterone in the urine. These authors also encountered increase in renin activity and in aldosterone excretion in the urine in malignant hypertensive disease, chronic pyelonephritis, and in the terminal phase of chronic glomerulonephritis.

Arterial pressure in most patients with chronic renal insufficiency may be maintained at the normal level by repeated dialysis for removing the excess of sodium and the water bound with it. These measures prove ineffective in some patients. They develop severe hypertension, the typical signs of which are a high content of renin, angiotensin II and I, and aldosterone in the blood. The removal of water and electrolytes during dialysis is attended by a still greater increase in the activity of renin and angiotensin in the blood of these patients and further increase of arterial pressure. Angiotensin in the patients probably has a direct pressor effect on the vessels. The blood renin and angiotensin content falls sharply immediately

after bilateral nephrectomy, while arterial pressure drops to normal level.

The prescription of spironolactones to such patients does not lead to a decrease of arterial pressure though it allows hypokaliaemia to be corrected. Their inefficacy is evidently determined by the fact that hyperaldosteronism is not the primary cause of hypertension but is of secondary character. The amount of metabolizable sodium in the body of these patients does not increase, spironolactone therapy only reduces its content and usually causes a mild decrease in arterial pressure.

High blood renin activity is the only reliable laboratory sign by means of which this form of arterial hypertension can be distinguished from hypertensive disease with increased excretion of aldosterone in the urine and reduced activity of renin in the blood. The results of spironolactone therapy are important only as a preliminary diagnostic method which cannot replace the test for renin activity in the blood.

Arterial hypertension is encountered both in aldosterone-secreting tumours of the adrenal cortex described above and in primary renin-secreting renal tumours. Renin hypersecretion (Conn's 'primary reninism') is accepted as the principal cause of arterial hypertension in *haemangiopericytoma* (a tumour arising from the juxtaglomerular cells of the nephron) and in *Wilms' tumour.*

Arterial hypertension in such cases may be of vascular or endocrine origin. In the first instance it is consequent upon compression of the renal artery by the growing tumour, in the second it results from secretion of pressor substances by the tumour into the blood. A large amount of renin was discovered in the tissues of these tumours. An explant of the tumour in a tissue culture continues producing renin.

It is very difficult to establish the diagnosis of haemangiopericytoma because it is very small and grows extremely slowly. Wilms' tumour grows far more rapidly and presents no diagnostic problem. Removal of haemangiopericytoma or Wilm's tumour results in the disappearance of arterial hypertension.

Catecholamine hypersecretion. Tumours of the adrenal cortex are rated among rare diseases. They account for 0.3 to 0.5 per cent of all cases with arterial hypertension. The tumour arises from chromaffin tissue. In approximately 90 per cent of cases it is localized in the adrenals, in 10 per cent it grows in other organs, namely, in the aortic paraganglia and particularly often in Zuckerkandl's bodies, in the carotid bodies, ovaries, testes, spleen and the wall of the urinary bladder.

Tumours localized in the adrenals and the wall of the urinary bladder secrete epinephrine and norepinephrine. Tumours of other localizations secrete only norepinephrine. According to the character

of growth, the tumour may be benign (*phaeochromocytoma*) or malignant (*phaeochromoblastoma*). Tumours of the adrenal medulla are usually unilateral and benign in most cases.

The clinical picture of phaeochromocytoma is determined by excessive supply of epinephrine and norepinephrine into the blood. The periodical release of large amounts of these amines into the blood is attended by paroxysms of palpitation, arterial hypertension, headache and profuse perspiration. The paroxysmal form of arterial hypertension is encountered in about one third or half of all cases with phaeochromocytoma. In the remaining cases with this disease arterial pressure is permanent. Its underlying factor is the continuous entry of large amounts of catecholamines into the blood. An asymptomatic course of the disease is encountered in rare cases.

Paroxysms of arterial hypertension are among the most characteristic symptoms of phaeochromocytoma. At first they are rare and mild. With the growth of the tumour the paroxysms become more frequent and may occur every day. In most cases they appear with no apparent cause. Sometimes their connection with emotional disturbances, physical exertion or other stress situations can be revealed. The clinical picture of the paroxysm is particularly manifest in children.

The attacks take place suddenly. Paraesthesia, the feeling of alarm and unfounded fear, and profuse perspiration appear first. Headache develops at the peak of the attack in 55 per cent of patients. In about 15 per cent of cases dizziness is encountered simultaneously. Palpitation is the second symptom of paroxysm in frequency. It is found in 38 per cent of cases. Increase of arterial pressure sometimes to 200-250 mm Hg is attended by retrosternal pain. Neither serious disorders of the heart rhythm, nor electrocardiographic signs of coronary insufficiency usually appear during a paroxysm.

Abdominal pain is often felt during an attack. Vomiting sometimes occurs at the peak of the pain. Hyperglycaemia and moderate neutrophilic leucocytosis with a shift to the left are regular occurrences at the height of an attack. Attacks of moderate severity last several hours. Profuse perspiration and polyuria are observed after arterial pressure falls to normal level. General weakness at the end of the attack depends on its severity and may last several hours to several days.

Extremely high elevation of arterial pressure during an attack may cause pulmonary oedema and cerebral haemorrhage, especially in the elderly. Haemorrhage into the adrenal occurs in rare cases, which may be attended by spontaneous recovery. Typical paroxysmal elevations of arterial pressure make identification of the true cause of hypertension much easier.

Permanent hypertension is found in more than half of patients with phaeochromocytoma. In some cases arterial pressure rises periodically in imitation of hypertensive crises typical of benign hypertensive disease; in others it remains permanently high as is the case in malignant hypertension. Hypertension appearing in children or young persons raises no doubts as to its symptomatic origin. It is far more difficult to detect the association of arterial hypertension with phaechromocytoma in elderly people. Frequent fainting, particularly when the patient gets up from bed very quickly, is a certain sign of such an association. Such transient loss of consciousness in ordinary hypertonics occurs only when they take hypertensive drugs. Certain significance should also be attached to the tendency of these patients to faint during anaesthesia or in minor surgical operations, e.g. extraction of a tooth. Sometimes they have diffuse hyperpigmentation of the skin or café-au-lait spots on it.

The urinary syndrome is manifested by proteinuria and microhaematuria which are found only during a paroxysm of hypertension at first but are permanent later. Permanent proteinuria was found in severe cases. To identify its causes, complete urological examination (pyelography, pneumoren, and kidney tomography) is conducted during which signs of a tumour of one or both adrenals are discovered.

Pharmacological tests with histamine, phentolamine or tropaphen have no practical value. Great diagnostic significance is attached to the results of direct determination of the rate of catecholamine secretion in the body. The daily catecholamine excretion in the urine in patients with phaeochromocytoma is always increased, particularly sharply on the days of hypertensive crises. Increased excretion of dopamine, dopa, and vanilmandelic acid is also recognized as an important sign.

Phaeochromocytoma with paroxysms of hypertension often has to be differentiated from the diencephalic syndrome which is also marked by periodic attacks of vegetative disorders with general nervousness, increased arterial pressure, headache, tachycardia, and hyperglycaemia. Increased excretion of catecholamines or vanilmandelic acid in the urine is a characteristic symptom of phaeochromocytoma. Disorders of carbohydrate, fat or water-electrolyte metabolism and increased intracranial pressure developing in attendance to the attack indicate that they are associated with the diencephalic syndrome.

The localization of the tumour is determined by instrumental examination. Intravenous urography reveals no more than one fourth of all tumours because compression of the upper pole of the kidney or displacement of the kidney which is demonstrated by this method is only caused by large tumours. Pneumorenography, which is usually performed together with urography, and tomography, are

more reliable diagnostic methods. Aortography, thermography and scintigraphy of the adrenals have been used with success in the recent years.

Phaeochromoblastoma accounts for about 10 per cent of all adrenal tumours. It is also marked by increased catecholamine production but its symptoms differ noticeably from those of phaeochromocytoma. Like any malignant new growth, it metastasizes. Metastasis occurs to the regional retroperitoneal lymph nodes. Growth of the tumour into the surrounding tissues as well as growth of the metastatic material lead to the appearance of pain in the abdomen or small of the back. Growth of the tumour is attended by elevated body temperature, increased ESR, and loss of body weight. Metastasis to the liver, bones, and lungs occurs in later stages.

Drug hypertension. When taking the medical history, the physician finds out what drugs the patient had received. Despite the different mechanisms, the end result of the action of some drugs proves to be the same: their regular use leads to elevation of arterial pressure. Giving preference to practical interest over academic propriety, we separated this form of hypertension caused by these drugs from all the other forms.

Contraceptives are the most common cause of drug hypertension in our times. Their regular and long-term use aggravates the course of already existing hypertension and may even induce stable hypertension in previously healthy females. Hypertension disappears when the agent is discontinued.

Liquorice powder is often used for treating peptic ulcer and constipation. Long-term medication with large doses of this drug sometimes leads to arterial hypertension developing against the background of hypokaliaemia. Clinical manifestations of hypokaliaemia such as muscle weakness and polyuria appear in severe cases. The clinical picture of this hypertension has many signs resembling those of Conn's syndrome, but aldosterone excretion in the urine is normal. Liquorice hypertension disappears soon after the drug is discontinued.

Long-term administration of steroid hormones sometimes leads to arterial hypertension together with which centripetal obesity and other signs of Itsenko-Cushing's syndrome usually develop. Arterial hypertension disappears soon after the drug is stopped. To avoid making a diagnostic error and mistaking these forms of hypertension (which is in essence iatrogenic) for hypertensive disease, it is necessary to always ask the patient whether he takes drugs capable of inducing elevation of arterial pressure.

Supplement IV-1

Causes of Arterial Hypertension

I. Hypertensive disease.
II. Symptomatic hypertension.
  A. Renal hypertension.
    1. Chronic pyelonephritis.
    2. Polycystic disease and other congenital anomalies of the kidneys.
    3. Diabetic glomerulosclerosis.
    4. Chronic glomerulonephritis.
    5. Obstructive uropathies.
    6. Vesicoureteral reflux.
    Stones in the ureters and kidneys.
    Inflammatory strictures of the urethra and ureters.
    Compression of the urinary tract by tumours, cysts, and cicatrizing connective tissue.
    Congenital anomalies of the urinary bladder, urethra, and ureters.
    Cicatricial deformity of the kidneys in tuberculosis.
  B. Vascular forms of hypertension.
    1. Renovascular hypertension.
    Atherosclerosis of the renal arteries.
    Fibromuscular hyperplasia of the renal artery.
    Developmental anomalies of the renal arteries.
    2. Arteritis of the aorta and its branches.
    3. Coarctation of the aorta.
    4. Periarteritis nodosa.
  C. Endocrine forms of hypertension.
    1. Mineralocorticoid hypersecretion.
    Conn's syndrome (primary hyperaldosteronism).
    Adrenal adenocarcinoma.
    Hypersecretion of other mineralocorticoids.
    2. Renin hypersecretion.
    3. Catecholamine hypersecretion.
    4. Glucocorticoid hypersecretion.
  D. Other (rare) diseases.

Chapter V

Ascites

Accumulation of fluid in the peritoneal cavity is called ascites. With the accumulation of a great amount of fluid in the peritoneal cavity within a short time (as in acute thrombosis of the main trunk of the portal vein) the abdomen becomes round and its skin tense and shiny. Diffuse tenderness of the skin of the abdomen to palpation is characteristic. When the fluid accumulates gradually in the peritoneal cavity (as in portal cirrhosis) the lower ribs are displaced forward and upward and the lower part of the thoracic cavity and the epigastric angle become wider. In accumulation of fluid in the peritoneal cavity, the diaphragm does not participate in the act of respiration.

The appearance of the abdomen in ascites depends on the patient's position in bed. When he lies on his back the fluid moves to the flanks of the abdomen causing their bulging. When the patient lies on the side the fluid accumulates in the low-lying half of the abdomen. When the patient stands or sits, the hypogastrium and ileal regions of the abdomen are most distended. The umbilicus is often everted. Dilatation of the superficial veins around the umbilicus is characteristic of ascites incident to portal hypertension. Dilatation of the superficial veins of the entire abdomen and lower chest is only encountered in thrombosis of vena cava inferior.

Accumulation of fluid in the peritoneal cavity is disclosed more simply by percussion. When the patient lies on his back, the fluid is found in the posterior (lower) parts of the peritoneal cavity while the air-containing intestine floats to the surface of the fluid. The percussion sound is tympanic over the anterior (upper) abdominal surface and dull over the flanks. Displacement of the zones of tympany and dullness in changes of the patient's position in bed is of highest diagnostic value. With the patient lying on his right side, the tympanic sound is elicited over the left flank; when he turns over to the left side, the sound is produced over the right flank.

Tympany is produced over the entire abdominal surface (when the patient is in a supine position) until approximately 1.5 to 2 l of fluid accumulates in the peritoneal cavity. Lesser amounts of fluid are not revealed by percussion. In all cases it is very important to examine the abdomen immediately after the removal of fluid. This often reveals tumours and changes in the size and consistency of the abdominal organs.

The fluid in the peritoneal cavity may be a filtrate of the blood serum or lymph (transudate), or it may be an exudate forming in inflammation of the peritoneum itself. The fluid may be serous, haemorrhagic, chylous or purulent. In most cases it is serous. Haemorrhagic fluid is mostly encountered in tuberculosis, malignant tumours and scurvy. When the ascitic fluid looks like milk, the condition is called chyliform ascites. It forms as a result of entry of large amounts of lymph into the peritoneal cavity from the thoracic duct or the lymph vessels in the abdominal cavity. The chylous fluid is sterile, contains a large number of lymphocytes and separates into layers on standing.

Paracentesis is valuable not only because it helps to reveal the character of the ascitic fluid, but also because it provides a possibility for its cultivation, determination of its cell composition and palpation of the organs of the abdominal cavity and pelvis.

Laparoscopy, during which biopsy may be performed, is now often resorted to simultaneously with removal of the fluid. Some authors recommend performing laparoscopic cholangiography and splenoportography, but these methods of examination have become less popular lately because they are hazardous for health.

The transudate differs from the exudate in the specific gravity and protein content of the ascitic fluid. Fluid containing more than 0.3 g/l protein and with a density above 1015 is considered an exudate. The fluid is regarded to be a transudate when its relative density and protein content are lower than the values given above.

On the basis of clinical experience, it may be stated that these diagnostic criteria of a transudate and exudate cannot be considered a reliable support for the diagnosis of peritonitis. Quite often one becomes convinced that ascitic fluid of a patient with heart failure contains more than 0.3 g/l of protein. It is also known that the ascitic fluid in tuberculous peritonitis sometimes proves to be a transudate. Though the criteria mentioned above are arbitrary, they are nonetheless valuable and in cases with a very high or very low protein content they make it possible to reliably distinguish inflammatory diseases of the peritoneum from diseases of other organs.

Great diagnostic significance is also attached to cytological examination of the ascitic fluid. The ascitic fluid is called haemorrhagic when it contains a great number of red blood cells. It is often found in cases with neoplasma, particularly of the liver and ovary, in tuberculous peritonitis, pancreatitis, acute thrombosis of the portal vein and in injuries to the abdominal organs. If 1 ml of ascitic fluid contains more than 250 leucocytes, inflammation of the peritoneum or its infiltration by a tumour may be assumed.

Prevalence of neutrophils is considered to be characteristic of acute bacterial peritonitis, whereas predominance of lymphocytes, of chronic peritonitis and particularly of tuberculosis. A high con-

tent of eosinophils in the ascitic fluid is an important diagnostic sign of eosinophilic enterocolitis. Cytological examination allowed ascites caused by a malignant tumour to be recognized in 60 to 90 per cent of cases. The results of this examination depend to a great measure on the volume of ascitic fluid sent to the laboratory.

Identification of Ascites

Accumulation of fluid in the peritoneal cavity is the most common but not the only cause of distension of the abdomen and stretching of its walls. The other causes of abdominal distension are listed in Supplement V-1.

Intestinal distension by gases occurs in many diseases. Sharp distension of the large intestine in ulcerative colitis and distension of the proximal intestinal segment in ileus are particularly hazardous. Diffuse distension of the small intestine in the sprue syndrome is also well known. The abdomen of such patients protrudes sharply forward and the contours of the intestine and even its peristalsis may sometimes be seen through the stretched abdominal wall. There is no fluid in the abdominal flanks in these patients. The percussion sound over the flanks is just as tympanic as the sound over the anterior abdominal wall.

When the distended intestinal loops contain both gas and fluid, it becomes very difficult to distinguish the condition from ascites only by the results of physical examination. X-ray examination is valuable in such cases. Accumulation of fluid and gas in the distended loops is demonstrated on a radiograph as multiple levels (Claubert's cups) which are best seen on radiographs taken with the patient in a vertical position.

Free fluid in the peritoneal cavity never forms Claubert's cups but produces diffuse shadowing of the abdominal cavity. On radiographs taken with the patient in a vertical position, the intensity of this shadow grows in the direction of the true pelvis. Widening of the shadow between the lateral margin of the colon and the peritoneum or soft tissues adjoining it is a characteristic sign of ascites. The width of these linear shadows in a healthy person does not exceed 1-2 mm.

Accumulation of large amounts of fluid in the peritoneal cavity prevents palpation of the lower hepatic margin. The right hepatic lobe becomes impalpable earliest of all. Distension of the intestine by gases does not hinder palpation of the liver.

An **ovarian cyst** and sometimes a **cyst of the mesentery** or a **retroperitoneal cyst** may occupy the entire peritoneal cavity in which case it is very difficult to distinguish them from ascites. The existence of a cyst should always be suspected when the abdomen has an

asymmetric shape uncharacteristic of ascites or when percussion of the abdominal flanks with the patient lying on his back elicits a tympanic sound while percussion of the anterior abdominal wall produces a dull sound.

When a patient with ascites assumes a vertical position, the free fluid in the peritoneal cavity accumulates mainly in the lower abdomen which protrudes noticeably. When the patient lies on his back, the abdomen becomes noticeably flatter because the free fluid is displaced to the flanks. When a patient with an ovarian cyst assumes a vertical position, the lower part of her abdomen protrudes obviously more than the upper part. The predominant protrusion of the lower abdomen ('bulging abdomen') does not disappear when the patient takes any position in bed.

Without denying the benefit of these differential diagnostic signs we became convinced that the most reliable information may be obtained from the results of bimanual gynaecological examination. It allows the diagnosis of an ovarian cyst to be made even when it exists simultaneously with free fluid in the peritoneal cavity.

The results of X-ray of the intestine with the use of a barium enema are also very important in making the differential diagnosis. In ascites the colon is in its usual position, whereas in a patient with a cyst of the ovary or mesentery, it stretches on the periphery of the abdominal cavity and in part follows the contours of the cyst compressing it. The highly raised transverse colon is particularly noticeable, its middle part is sometimes seen even above the hepatic flexure.

The abdomen is sometimes markedly enlarged in severe obesity. In some of our patients suffering from the diencephalic syndrome with adiposity and oedema of the subcutaneous tissue the abdomen was so distended that among the results of all physical methods of examination only a retracted umbilicus pointed to the absence of ascites.

Prolonged medication with diuretics sometimes leads to marked flatulence of the abdomen. We encountered this complication in chronic circulatory insufficiency and coeliac disease. With the prescription of potassium preparations abdominal flatulence reduces sharply and the true size of the ascites may be determined. Marked abdominal flatulence is sometimes observed in myxoedema, ulcerative colitis, acute pyelonephritis and severe gastroenteritis. In myxoedema it is combined with the accumulation of usually a small amount of fluid in the peritoneal cavity.

There are hysterical women of child-bearing age who sometimes develop such marked enlargement and distension of the abdomen that young physicians make an erroneous diagnosis of pregnancy, ovarian cyst or ascites. The distension of the abdomen in such instances is caused by contraction of the abdominal-wall muscles

with simultaneous downward displacement of the diaphragm. When the patient lies supine with the lower limbs flexed at the hips and knees, abdominal distension rapidly disappears without passage of gases. The normal shape of the abdomen is restored (also without passage of gases) by subcutaneous morphine injection, during sound sleep, or under short-term anaesthesia. It proves far more difficult to persuade patients to agree to such manipulations, than to perform them.

Distension of hollow organs localized in the abdominal cavity is sometimes mistaken for ascites. In instances of acute distension, the stomach may fill the whole abdominal cavity. This complication is always attended by collapse and sometimes leads to spontaneous rupture of the stomach. Acute distension of the stomach develops mostly in tumour of the pylorus, acute lobar pneumonia, and other severe infectious diseases. Some authors reported cases of acute distension of the urinary bladder which was so considerable that it was mistaken for ascites.

Causes of Ascites

Ascites is encountered both in diseases of the peritoneum itself and in diseases of other organs and systems. Cirrhosis of the liver, metastasis of malignant tumours to the peritoneum, heart failure and tuberculous peritonitis are its most common causes (Supplement V-2). Of the total number of cases with ascites the origin of which was not obvious, 60-65 per cent were induced by cirrhosis and about 30 per cent by tumours. In other diseases ascites is a rare occurrence. Ascites in most cases of diseases of the heart, kidneys, and gastro-intestinal tract is merely one of the indications that disorders of water-electrolyte metabolism characteristic of these diseases have developed. Its cause is usually obvious and no special examination is needed.

In principle, ascites may develop in any inflammatory disease of the peritoneum, but because of the rapid course followed by most of these diseases, marked and long-term ascites is encountered only in **tuberculous peritonitis.** Its clinical manifestations are very diverse. In most cases it begins insidiously. Only moderate fever, rapid fatiguability and loss of body weight trouble the patient for some time. About half the patients complain of abdominal pain which has no definite localization, as a rule, and is not very intensive.

Ascites is the principal objective sign of this form of tuberculous peritonitis. It is found in approximately 75 per cent of cases. The abdominal wall is moderately tender. Muscular rigidity is absent, as a rule. Deep palpation of the abdomen is therefore possible and

in approximately 20 per cent of cases a tumour is revealed. A tumour that is an inflamed mesentery, is immobile.

An inflamed omentum rarely retains its mobility; in most instances it adheres to other abdominal organs. An enlarged liver is palpated in about one fourth of the patients. Enlarged lymph nodes are sometimes found. The tuberculin tests are positive in some cases and negative in others. The blood changes are inconstant. The blood leucocyte count is normal in 70 to 90 per cent of cases. Anaemia is sometimes found.

Non-specific character of the clinical manifestations of tuberculous peritonitis makes the diagnosis noticeably difficult. The existence of tuberculous peritonitis should be assumed in each case of isolated ascites following a course with fever, dull, indefinitely localized pain in the abdomen, and loss of body weight. Considerable significance should also be attached to the patient's age. It is young individuals who suffer from tuberculous peritonitis, as a rule. Symptoms of tuberculous affections of other organs obviously support the assumption that the case is that of tuberculous peritonitis, although naturally they cannot be regarded as proof of it.

Examination of the ascitic fluid sometimes helps greatly in the diagnosis. In 85 to 100 per cent of cases it proves to be an exudate with a high leucocyte count for 80 per cent of which mononuclear cells are responsible. *Mycobacterium tuberculosis* culture is produced in no more than 40 to 80 per cent of cases.

The findings of laparoscopy may be of great diagnostic aid, particularly if it is combined with purposeful biopsy. Unfortunately, tuberculous peritonitis is often marked by a large number of adhesions in the abdominal cavity which make the examination difficult or impossible. That is why even today all the methods mentioned above allow the diagnosis of tuberculous peritonitis to be made in approximately 80-85 per cent of patients. In the remainder of cases the results of these methods provide grounds for making only a tentative diagnosis with a certain margin of probability. The final diagnosis of the disease in 15 to 20 per cent of cases may be established only after exploratory laparotomy which makes it possible, in the process, to determine the origin of a tumour frequently palpated in the abdominal cavity.

Isolated, irrepressibly growing ascites is the main symptom of **mesothelioma**, a rare tumour arising from the epithelial and mesenchymal elements of the peritoneum. Growth of the ascites is attended by abdominal pain, recurrent vomiting, anorexia and loss of body weight. The disease sets in after the age of 40; males and females are afflicted with the same frequency. The tumour hardly ever metastasizes. The diagnosis may only be based on the results of laparotomy or laparoscopy.

Bacterial and fungal infection of the peritoneum usually produces

the clinical picture of acute abdomen. Laparotomy in such instances is usually performed before ascites has time to develop.

Metastasis of a malignant tumour to the peritoneum is the most common cause of ascites among peritoneal diseases. The primary tumour is usually localized in the stomach, intestine, pancreas, liver, ovary or uterus. Metastasis may also appear many years after the primary tumour had been removed. Serous or haemorrhagic fluid gradually accumulates in the abdominal cavity; tumour cells are sometimes found in this fluid. Just as in tuberculous peritonitis, the fluid may be an exudate in some cases and a transudate in others. The sediment contains many red blood cells, lymphocytes, neutrophils and endothelial cells.

There are no noticeable changes in the patient's general condition in the early period of ascites. Body temperature is normal. Hypoproteinaemia and cachexia appear later. Mild oedema of the lower limbs is often found. Death occurs from emaciation or complications (ileus, perforation, infection, thrombophlebitis).

The cause of ascites is obvious when the localization of the primary tumour is known. Difficulties in the diagnosis arise only in cases with isolated ascites, because it may be a consequence of the dissemination of a malignant tumour in the peritoneum or of tuberculous peritonitis, mesothelioma, cirrhosis of the liver and many other diseases. Laparoscopy reveals either millet-like lesions resembling those in tuberculosis of the peritoneum or true metastasis of carcinoma on the surface of the peritoneum and omentum.

With gradual growth of the carcinomatous nodules, the involved omentum becomes macrogranular, wrinkled and is found under the greater curvature of the stomach where it is palpated as a tumorous mass. X-ray examination, however, does not demonstrate a tumour stomach and only laparoscopy or laparotomy discloses the true condition of the abdominal organs.

Ascites is the dominating syndrome in **peritoneal pseudomyxoma**, which is mostly encountered in cases with benign cyst of the vermiform process and cystadenoma or cystadenocarcinoma of the ovary. It is found much less frequently in cases with other tumours: fibroma of the ovary, teratoma of the ovary, carcinoma of the uterus and common bile duct, urachus, mucous adenocarcinoma of the large intestine, mucous omphalomesenteric cyst of the umbilicus.

The disease begins with gradual enlargement of the abdomen and loss of body weight. In some cases the ascitic fluid does not differ from exudates of other origin in composition and appearance; sometimes it is a gelatinous mass discharged with difficulty or not at all (as it was observed in a case in our practice) through the trocar opening. The diagnosis can be established only after laparotomy.

Just as other tumours, peritoneal pseudomyxoma is mainly encountered in individuals after the age of 40.

Portal hypertension. The term 'portal hypertension' is used to designate a complex of signs occurring in impaired circulation in the portal system. High blood pressure in the portal vein, splenomegaly, varicose veins of the oesophagus, stomach and abdominal wall, gastro-intestinal haemorrhage and ascites are the main symptoms of portal hypertension. For the purpose of differential diagnosis, separation of portal hypertension into three types as suggested by Patsiora (1974) is most convenient. We resorted to this, although in a simplified form.

Thrombosis of the hepatic veins, isolated or combined with thrombosis or stenosis of vena cava inferior. Thrombosis with total obstruction of some or most of the hepatic veins is encountered both as an isolated disease and in combination with thrombosis of the vena cava inferior. In the latter case the thrombus forms in the vena cava inferior and spreads to the hepatic veins.

Thrombosis of the hepatic veins is usually a complication of primary carcinoma of the liver, hypernephroma, polycythaemia, generalized thrombophlebitis, and prolonged medication with oral oestrogenic contraceptives. The experimental model of the disease is reproduced by prescribing monocrotaline contained in plants found all over the world.

The acute form of the disease occurs as a complication of polycythaemia, carcinoma of the liver or thrombophlebitis. Abdominal pain and vomiting appear suddenly in a patient suffering from one of these diseases. Objective examination reveals hepatomegaly, ascites and often mild jaundice of the skin. If all or most of the veins are obstructed the disease terminates in death from hepatic coma.

In less acute cases only enlargement of the liver, abdominal pain caused by stretching of Glisson's capsule, and ascites are encountered. With time and the gradual growth of portal hypertension the veins of the oesophagus and stomach become dilated and enlargement of the spleen is noted. The appearance of oedema of the lower limbs and a network of dilated subcutaneous veins on the abdomen indicates that concomitant thrombosis of vena cava inferior has developed. After paracentesis, the ascitic fluid gradually accumulates, the liver and spleen stay enlarged, becoming harder with time and their margin is no longer tender to palpation.

In the acute period of the disease needle biopsy discloses increased blood filling of the liver with sinusoidal dilatation and necrosis of the hepatic cells around the lobular vein, i.e. a picture of acute nutmeg liver characteristic of heart failure and constrictive pericarditis. According to the results of cavagraphy, vena cava inferior is not obstructed. Transcutaneous hepatography with injec-

tion of the contrast medium into the liver demonstrates blocking of the hepatic veins, but this method failed to receive wide application in the clinic. Scanograms of the liver usually show ischaemic areas corresponding to the channel of the obstructed branches of the hepatic veins.

The clinical picture of the disease to a great measure resembles the picture of right-ventricular insufficiency, constrictive pericarditis, cirrhosis of the liver, thrombosis of the portal vein and its branches, and thrombosis of vena cava inferior. The differential diagnosis between thrombosis of the hepatic veins and acute right-ventricular insufficiency cannot be regarded as difficult. Both diseases set in with acute pain in the right hypochondrium which is soon attended by hepatomegaly, mild jaundice and moderate ascites. Although both diseases begin acutely, right-ventricular insufficiency is always a complication of a long-existing heart disease, usually mitral stenosis or cardiosclerosis. It occurs either after great physical exertion or under the effect of acute complications, e.g. an attack of cardiac fibrillation or thromboembolism of the pulmonary artery. Electrocardiography and X-ray always disclose signs of a heart disease or pulmonary hypertension. These signs are not found in thrombosis of the hepatic veins.

Vena cava inferior thrombosis is manifested by a clinical picture which differs from that of thrombosis of the hepatic veins in the absence of ascites and the presence of signs of developed collateral circulation between venae cavae inferior and superior. Drastically dilated subcutaneous veins are mainly found on the lateral surfaces of the abdomen. The blood in these veins flows in an ascending direction (from the bed of vena cava inferior into the bed of vena cava superior). Pressure in vena cava inferior distal to the site of the thrombosis is always elevated, and a characteristic dilatation of the vein before the place of its obstruction is seen on the cavagram.

Thrombosis of the hepatic veins is sometimes combined with stenosis or even occlusion of vena cava inferior. In such cases cavacaval anastomoses begin developing simultaneously with ascites. They differ from portacaval anastomoses forming in cirrhosis of the liver in localization and the direction of the blood flow in them. Combined affection of the hepatic veins and vena cava inferior should be suspected in all cases of manifest cavacaval anastomoses. The site of vena cava inferior stenosis or obstruction is determined from the results of inferior and superior cavagraphy.

Obstruction or stenosis of the portal vein and its branches. Stenosis and even total obstruction of the portal vein or its branches may be congenital or may develop after birth. Umbilical sepsis and pylephlebitis are the most common causes of obstruction of the hepatic vein in early childhood. At an older age pylephlebitis may

be a complication of abdominal trauma, osteomyelitis and purulent appendicitis. In rare instances thrombosis of the hepatic vein develops in a patient with cirrhosis of the liver with no obvious cause.

Thrombosis and constriction of the portal vein are often encountered in metastasis of malignant tumours to the lymph nodes in the porta hepatis. This is a particularly constant occurrence in primary hepatoma and carcinoma of the pancreas, stomach and large intestine. A similar mechanism of portal hypertension occurs in abscesses in the porta hepatis and in compression of the portal vein and its branches by enlarged lymph nodes, e.g. in lymphogranulomatosis. Thromboses of the portal vein are among the typical complications of polycythaemia.

The clinical picture of thrombosis of the portal vein and its branches is fairly monotonous. It comprises splenomegaly and varicose veins of the oesophagus and stomach. Gastric haemorrhages appear in the later developmental stages of the disease. The disease prevails among children and young people. According to Patsiora (1974), 72 per cent of such patients encountered in her experience in the surgical clinic were under 30 years of age. Older patients with this disease are met with somewhat more frequently in clinics for internal diseases.

Enlargement of the spleen and often pancytopenia are found (usually by chance) during the course of the principal disease (e.g. pylephlebitis) or some time after recovery from it. The longer the duration of splenomegaly, the more often disorders of hepatic function are revealed, e.g. its excretory function (Sherlock, 1971). The size of the liver is determined by the character of the principal disease. Splenoportography makes it possible to determine the pressure level in the portal vein system and appraise the state of collateral circulation.

The period of splenomegaly is asymptomatic in approximately 28 per cent of cases and gastro-intestinal haemorrhages usually prove to be first the clinical manifestation of the disease. This haemorrhage is profuse as a rule, and is often mistaken for a haemorrhage from a gastric ulcer.

Thrombosis of the portal vein and its branches is sometimes taken erroneously for thrombocytopenic purpura (Werlhof's disease). This unusual resemblance between two different diseases is explained by the development of hypersplenism in long-term splenomegaly and the appearance of bleeding from the nose and, in some cases, from the uterus in thrombosis of the portal vein branches.

These two diseases differ most sharply in the medical history, the size of the spleen, condition of the eosophageal veins and in the character of the bleeding. Haemorrhages in portal hypertension occur periodically and are distinguished by their abundance and sudden occurrence. Both before the bleeding begins and in the interval

between two bouts of bleeding the patient feels practically healthy and no signs of increased tendency to bleeding are found. Thrombocytopenic purpura does not produce massive gastro-intestinal haemorrhages. It is marked by ecchymoses and punctate haemorrhages into the skin which persist during nasal bleeding and after it is arrested.

An enlarged spleen is a constant sign of portal hypertension. During profuse bleeding it may grow smaller, but remains enlarged in the interval between two haemorrhages. In thrombocytopenic purpura the spleen is enlarged only during exacerbation of the disease. The pressure in the portal system is always increased in thrombosis of the portal vein but invariably normal in thrombocytopenic purpura. Varicosity of the eosophageal veins is never encountered in thrombocytopenic purpura, but is one of the compulsory causes of gastro-intestinal haemorrhage in thrombosis of the portal vein branches. It may be detected in the interval between two haemorrhages by oesophagoscopy or X-ray.

Ascites sometimes develops after haemorrhage in patients with portal hypertension of long standing, but never appears in thrombocytopenic purpura. Dilatation of the subcutaneous veins on the abdominal wall is encountered in portal hypertension, but never in thrombocytopenic purpura. The differential diagnosis between thrombosis in the portal vein bed and thrombocytopenic purpura may be made at the patient's bedside and we never found it necessary to resort to special methods of examination.

Diseases of the liver. Portal hypertension is mostly caused by intrahepatic blocking of the blood flow, which may be presinusoidal or post-sinusoidal. Presinusoidal portal hypertension is consequent upon congenital obstruction of the portal vein branches. Pressure in the hepatic vein proves to be normal, while that in the splenic vein is increased. Portal hypertension often develops in infiltration of the portal zones with myeloid tissue in myeloleucosis and myelosclerosis. A similar explanation is offered for portal hypertension in sarcoidosis and virus hepatitis. Portal hypertension in cirrhosis of the liver is always post-sinusoidal.

Patients with cirrhosis of the liver usually come for medical advice because of jaundice or enlargement of the abdomen and loss of body weight. Hepatomegaly is found on inspection. The spleen is found to be enlarged in some of the patients. The development of ascites is usually preceded by a period of dyspepsia during which abdominal flatulence and increased gas production in the intestine are encountered. Oedema of the lower limbs is mild and appears much later than ascites. By the time that ascites develops, varicosity of the oesophageal veins and signs of developed collateral circulation in the subcutaneous veins of the abdominal wall are already found.

Micronodular (portal) cirrhosis of the liver is encountered much more frequently than the other forms. It usually sets in gradually with anorexia and loss of body weight. Ascites is sometimes the first sign which makes the patient turn to a physician. By this time the liver is enlarged in most patients and the spleen in one half to one third of the patients. Gastro-intestinal haemorrhages appear later than ascites. Cirrhosis of the liver is sometimes marked by recurrent jaundice, pain in the region of the liver, and long-term fever. In such cases ascites appears in later stages of the disease. Primary biliary cirrhosis and haemochromatosis are complicated by ascites only in late stages so that its cause raises no diagnostic doubts.

Ascites often develops in the later stages of primary carcinoma of the liver which, in most cases, is incident to preceding cirrhosis. Ascites in such cases of carcinoma-cirrhosis develops both because of the intrahepatic blocking of the blood flow characteristic of cirrhosis and because of compression or thrombosis of the portal vein by the metastatic tumours. Such cases should be referred to as portal hypertension of combined (intra- and extrahepatic) origin.

Chronic thrombosis of the portal vein (e.g. in polycythaemia), just as cirrhosis of the liver, sometimes begins with the ascitic syndrome. Simultaneous enlargement of the liver may cause considerable diagnostic difficulties the overcoming of which is helped by systematic analysis of the following signs.

Thrombosis of the portal vein branches is often complicated by massive haemorrhage which may occur suddenly. Ascites develops only in the late stages of this disease. That is why, in taking the medical history, it is necessary to find out not only past infections, operations, injuries and complications, but the order in which the different signs and syndromes had appeared. Ascites may precede gastro-intestinal haemorrhage in cirrhosis and polycythaemia but it never develops earlier than the haemorrhage in acute thrombosis of the portal vein branches.

Paramount differential diagnostic importance must also be attached to the size of the spleen. It is markedly enlarged in each case of portal vein thrombosis, whereas in some patients with cirrhosis of the liver, its size, as determined by percussion and palpation, does not change. The liver is usually of normal size in thrombosis of the portal vein, whereas in cirrhosis it may be normal or smaller in size or enlarged. The consistency and character of the hepatic margin are often abnormal in cirrhosis, but are normal in portal vein thrombosis.

Splenic portography yields the most reliable information for distinguishing these diseases. In thrombosis of the portal vein occlusion of any of its branches or even of the large trunk is always

found, whereas in cirrhosis of the liver the portal vein and its branches are not obstructed.

The differential diagnosis of the syndromes that are compared may also be made by means of laparoscopy combined with biopsy. The cirrhotic liver is usually reduced in volume and its surface is formed by small nodules alternating with areas of connective tissue. The margin of the liver is always sharp and firm. Areas of perihepatitis are often found on the surface of the liver in cirrhosis. In portal vein thrombosis the surface of the liver is normal.

Signs of portal hypertension are encountered both in cirrhosis of the liver and in thrombosis of the portal vein branches. They comprise dilatation of the veins of the stomach, gall bladder, surface of the diaphragm and the ligamental apparatus of the liver.

Histologic examination of pieces of liver taken during laparoscopy or by needle biopsy in cirrhosis of the liver discloses characteristic changes in the lobular structure of the organ; in thrombosis of the portal vein the structure of the liver, in contrast, is normal.

The differential diagnosis of the syndromes may also be made from scintigraphy using colloidal gold. The scanograms show the size, shape, the uniformity of the blood filling of the liver, and the degree of extrahepatic colloidal gold uptake. In this stage of the disease when ascites develops the cirrhotic liver is reduced in size, as a rule (one lobe may be reduced and the other enlarged) and radioactivity of the different hepatic areas is not the same. Enlargement of the spleen and, quite often, increased bone marrow radioactivity are found on the scanograms.

In portal vein thrombosis the liver is normal in size and shape. Radioactivity on the different areas is always the same. Despite marked splenomegaly, radioactivity of the spleen in this disease is always much lower than in cirrhosis, while radioactivity of the bone marrow is almost never demonstrated.

The protein composition of the blood serum and the functional liver tests in the syndromes also differ frequently. Disorders of secretory hepatic function, reduced concentration of albumins, and increased content of gamma-globulins may be found in a patient with cirrhosis, at times long before ascites develops. In thrombosis of the hepatic vein these changes only appear in the late stages.

The differential diagnosis presents no difficulties when ascites appears in cirrhosis of the liver together with jaundice and the development of a network of subcutaneous collaterals. Unfortunately, this only happens in some cases of cirrhosis. In the most frequently occurring micronodular (portal) cirrhosis, ascites appears prior to

jaundice as a rule, and often before the development of varicosity of the subcutaneous veins on the chest and abdomen. This type of isolated ascites may also be incident to other diseases, mostly to diseases of the heart and the pericardium.

Ascites, anasarca, hepatomegaly and jaundice of the skin are often encountered in right-ventricular insufficiency, which has to be differentiated from cirrhosis of the liver in such cases. In severe heart failure with long-term ascites, enlargement of the spleen is often found as well as hypoproteinaemia caused by a reduced content in the blood of albumins mainly. The graver heart failure, the more marked are the signs of liver involvement and the easier (though it may seem a paradox) it is differentiated from cirrhosis of the liver. This is explained by the fact that anasarca, cyanosis, dyspnoea which often develops into orthopnoea, and other characteristic diagnostic signs of heart failure are more pronounced in its late stages. Cachexia with more or less uniform atrophy of the muscles of the entire trunk with no concomitant changes in the bone skeleton develops in the severest cases of heart failure. Prevalent atrophy of the chest muscles with characteristic widening of the epigastric angle are encountered in severe cirrhosis of the liver.

In cirrhosis of the liver the spleen is sometimes enlarged long before ascites develops. Its enlargement in the ascitic stage is found in no less than one third of patients. Splenomegaly is encountered only in the late stages of heart failure and only in patients with ascites of long duration. Dilated oesophageal veins are found only in cirrhosis of the liver.

The results of examination of the heart and its parts are extremely valuable in making the differential diagnosis. The character of changes in the ECG, cardiac sounds and murmurs, and blood pressure level in the arteries and veins in various diseases are described in detail in the chapter 'Heart Failure'. If it is taken into account that right-ventricular insufficiency is always attended by more or less marked pulmonary hypertension, the following rule may be formulated. The discovery of symptoms of pulmonary hypertension in a patient should make the diagnosis lean in favour of heart failure, while the discovery of signs of portal hypertension makes the diagnosis of cirrhosis of the liver more probable. In other words, signs of pulmonary hypertension are not encountered in cirrhosis, whereas signs of portal hypertension are not found in heart failure. The cited rule is equally just for all cases of mild and severe heart failure and for all cases of mild and for most cases of severe cirrhosis of the liver.

In **constrictive pericarditis** (just as in cirrhosis of the liver) ascites appears much earlier than anasarca. Both diseases are attended by hepatomegaly and splenomegaly and in far advanced stages are complicated by hipoproteinaemia mainly caused by reduced albumin

concentration. There is no enlargement of the heart in either of the diseases.

It is easy to distinguish constrictive pericarditis from cirrhosis by the venous pressure level, the characteristic changes in the heart sounds, the results of X-ray examination and the pronounced pattern of collateral circulation. These signs, unfortunately, are demonstrated far from in every instance of this disease.

In constrictive pericarditis, venous pressure is always sharply elevated, its level often exceeding 300 mm H_2O. Such high levels of venous pressure are never found in cirrhosis of the liver. X-ray signs of pericardial calcification may be encountered only in constrictive pericarditis. In each case of this disease an accessory cardiac sound is heard which, joining the main sounds, produces a characteristic triple rhythm of the heart.

Cardiac fibrillation is found almost in every far-advanced case of constrictive pericarditis. Roentgenokymography makes it possible to determine the absence of heart pulsation or reveals its drastically diminished amplitude. These signs do not occur in cirrhosis, and the detection of even one of them is evidence that the patient has constrictive pericarditis and not cirrhosis.

Diseases of the kidneys. Two main causes of ascites in renal diseases may be distinguished, namely, hypoproteinaemia and heart failure. Ascites is one of the symptoms of severe *nephrotic syndrome*. Besides ascites, these patients have anasarca and lose large amounts of protein in the urine and into the gastro-intestinal tract. In the terminal stage of chronic nephritis, ascites develops simultaneously with enlargement of the liver, elevation of venous pressure, severe dyspnoea, and other symptoms of heart failure.

The distinguishing feature of ascites in the nephrotic syndrome is that it develops always simultaneously or immediately after the other clinical and laboratory symptoms of this syndrome (anasarca, hypoproteinaemia, hypercholesterolaemia and proteinuria).

Diseases of the heart and pericardium. Some patients with *constrictive pericarditis* apply for medical advice for the first time because of an enlarged abdomen. Inspection discloses ascites which is sometimes isolated and at other times combined with mild skin pitting on the crura or malleoli. It has still not been revealed why marked ascites develops when anasarca is mild and at times even when there is no oedema. By the time that ascites develops, the liver in patients with constrictive pericarditis is enlarged and firm or even very firm.

Dyspnoea in these patients is very moderate or may be absent. Patients with constrictive pericarditis complain of rapid fatiguability, but not of dyspnoea. There is no pain in the region of the

heart as a rule. Chest pain (mostly in the right lateral region) is felt at times and is due to involvement in the process of the pleural layers on the right. In constrictive pericarditis, just as in cirrhosis of the liver and in Meigs' syndrome, ascites is often combined with accumulation of fluid in one or both pleural cavities.

The clinical picture of constrictive pericarditis with ascites, hepatomegaly and splenomegaly often resembles that of chronic heart failure in cardiomyopathy and myocarditis and the picture of cirrhosis of the liver. It is most difficult to distinguish constrictive pericarditis from heart failure developing in cardiomyopathy. Its differential diagnosis with cirrhosis of the liver is easier and can always be made without resorting to additional examination.

Ascites is always attendant to *severe right-ventricular insufficiency* which is encountered in an isolated form in cor pulmonale, congenital tricuspid disease, congenital developmental anomaly of the pulmonary artery, in tumours (e.g. myxoma) of the right heart, and in tumour metastasis (e.g. carcinoid tumour) to the structures of the right heart. It should be borne in mind that in heart failure ascites always appears later than oedema of the lower limbs and always only in cases with severe right-ventricular failure. Once developed, it usually persists for a long time. This distinguishes it from ascites in acute nephritis which may occur and disappear within two weeks, for example. Ascites may be the only manifestation of impaired water-electrolyte metabolism in cardiac cachexia. The identification of its cause in such cases is not difficult.

Diseases of the gastro-intestinal tract. Marked disorders of water-electrolyte metabolism in gastro-intestinal diseases develop under the effect of diarrhoea and hypoproteinaemia consequent upon increased loss of protein in the gastro-intestinal tract. In gastro-intestinal diseases oedema always appears simultaneously in the subcutaneous tissue and in the serous cavities.

In *Wipple's disease, eosinophilic gastroenteritis, Crohn's disease and coeliac disease* oedema and ascites develop in attendance to long-existing diarrhoea as if they are its late complications. Ascites in this type of impaired water-electrolyte metabolism is never isolated, and the identification of its cause usually presents no difficulties.

Intestinal lymphangiectasis is often complicated by anasarca and chylous ascites. Lymphangitis of the mesentery, induced by filarial parasites, is encountered particularly often in tropical countries. In the Soviet Union this disease has been completely eradicated. Acute and chronic forms of chylous ascites are distinguished. Acute chylous ascites often proves to be a complication of pancreatitis and injuries; the chronic form develops as a result

of compression or obstruction of the lymphatics by a tumour, haematoma, cicatricial tissue and inflamed mesenteric lymph nodes.

The causes of many cases of chylous ascites remain undisclosed. This is also true of ascites occurring in intestinal lymphangiectasis which may be congenital and, probably, acquired. Ascites and oedema in this disease are always encountered together with severe protein loss into the intestinal lumen.

Other diseases. Ascites may be predominant and sometimes the only clinical symptom of myxoedema and some diseases of the ovaries and pancreas.

In some cases of *myxoedema*, swelling of the mucopolysaccharides is so moderate that it is difficult for detection by routine physical methods of examination. Disorders of the intellect in such cases may also be very slight. Ascites proves to be the principal clinical syndrome. Some authors drew attention to the refractory character of this ascites. The prescription of diuretics, even in large doses, proves insufficiently effective. The ascitic fluid contains a great amount of protein (usually more than 40 g/l) which resembles blood serum protein in electrophoretic properties. It usually disappears in two or three weeks after the prescription of thyroidin.

Ascites is often combined with hydrothorax in benign and other *ovarian tumours* (Meigs' syndrome).

Meigs' syndrome is revealed in cases with fibroma and cystadenoma of the ovary with remarkable persistence. Ascites sometimes develops in females for whom clomiphene and similar agents stimulating ovarian function had been prescribed. Surgical removal of the tumour, or discontinuation of ovarian function stimulants results in disappearance of the ascites.

Ascites appears in some cases of *pancreatitis*. This happens in patients suffering from alcoholism. In such patients ascites usually develops after more or less intensive abdominal pain of various duration. Ascites proves to be very large and unresponsive to the prescription of diuretics. The content of amylase in the ascitic fluid is characteristically high. Enlargement of the pancreas and often a cyst are usually discovered during operation; removal of the cyst results in the disappearance of ascites. It disappears in some cases after paracentesis is performed just once. The protein content in the ascitic fluid usually does not exceed 25 g/l.

The differential diagnosis of ascites may be simplified if in taking the medical history and appraising the clinical course of the disease, the physician pays attention to the order in which ascites and anasarca appear and to their relative degree of severity.

Ascites appears before anasarca and remains either the only or the predominant syndrome for a considerable length of time in tu-

berculosis of the peritoneum, cirrhosis of the liver, constrictive pericarditis and Meigs' syndrome.

The rare causes of isolated ascites should not be forgotten either. These are primary peritoneal myxoma, peritoneal pseudomyxoma, myxoedema, pancreatitis and malignant tumours of the abdominal organs.

In gastro-intestinal diseases marked by the increased protein loss syndrome, and in renal diseases ascites usually develops at the same time as anasarca. The development of ascites after anasarca is considered to be characteristic of heart diseases. Combination of ascites with jaundice is encountered in cirrhosis of the liver, cirrhosis-carcinoma, and thrombosis of the hepatic vein. Subcutaneous portacaval collaterals develop in cirrhosis of the liver while a pattern of cavacaval collaterals is characteristic of stenosis or thrombosis of vena cava inferior.

A record kept of these signs makes planning of the further examination of the patient easier and facilitates rapid identification of the aetiology of the malady.

Supplement V-1

Causes of Abdominal Enlargement

1. Dilatation of the intestine.
2. Distension of the stomach.
3. Ovarin cyst.
4. Large mesenteric cyst.
5. Pregnant uterus with hydrops amnion.
6. Distended urinary bladder.
7. Obesity.
8. Phantom tumour (in hysterics).
9. Ascites.

Supplement V-2

Causes of Ascites

1. Primary diseases of the peritoneum.
   - Tuberculous peritonitis.
   - Other forms of peritonitis.
   - Mesothelioma.
2. Peritoneal affection in other diseases.
   - Carcinoma metastases.
   - Pseudomyxoma.
3. Portal hypertension.
   - Thrombosis of the hepatic veins.
   - Thrombosis or stenosis of vena cava inferior above or at the site of hepatic vein drainage.
   - Obstruction or stenosis of the portal vein and its branches.
   - Cirrhosis of the liver.
   - Tumour of the liver.

Other diseases of the liver.
4. Diseases of the kidneys.
Nephrotic syndrome.
Chronic nephritis.
5. Diseases of the heart and pericardium.
Constrictive pericarditis.
Right-ventricular cardiac insufficiency.
Cardiac cachexia.
6. Gastro-intestinal diseases.
Intestinal lymphangiectasis.
Wipple's disease.
7. Other diseases.
Myxoedema.
Meigs' syndrome.
Pancreatitis.

Chapter VI

Chest Pain

Chronic (Recurring) Pain

Protracted, or persistently recurring pains in the chest are so common that persons suffering from them come to the physician only if they become unbearable. Short-term attacks of pain are the predominant and the only symptoms of angina pectoris. When these attacks are rare, the patient is capable of working, but if they become frequent, a picture of a preinfarction state develops which calls for hospitalization.

Clinical examination alone is insufficient, as a rule, for identifying the causes of the pain in the chest. However sparse the results of the first clinical examination may be, they nevertheless form the basis for formulating the tentative diagnosis and planning further diagnostic work, which will noticeably reduce the time needed to identify the causes of pain. Negative results of a single examination should not discourage the physician. This happens often enough in angina pectoris, bronchial carcinoma and many other diseases the diagnosis of which can often be established after a more or less long follow-up of their course.

It is important to bear in mind that chest pains in one and the same patient may arise under the effect of not just one, but of two and even more factors. Attacks of chest pain, for instance, may be consequent upon simultaneously existing coronary insufficiency and osteochondrosis of the cervical spine. Psychogenic pain may occur in attendance to any organic disease of the thoracic organs. Neurotic pains may be spoken of only if the results of long-term surveillance allow the organic nature of the malady to be ruled out with assurance.

The following three types of chest pain are generally distinguished: pain resulting from stimulation of the peripheral nerves; pain caused by stimulation of the posterior roots of the spinal nerves, and pain from stimulation of the vegetative afferent fibres which are components of the sympathetic and vagus nerves. The combination of these pains with signs of affection of the osteomuscular apparatus and the organs located in the thoracic cage produces characteristic clinical syndromes. Syndromes arising in heart diseases are the most commonly encountered. The internist must be able to recognize these pains on questioning the patient and to distinguish them from extracardiac pain (Supplement VI-1).

Cardialgia

Angina Pectoris (Stenocardia)

The term 'angina pectoris' designates a group of clinical syndromes resulting from inability of coronary circulation to provide the heart muscle with nurtients in amounts that are adequate to its needs. The causes for this may be: stenosing atherosclerosis of the coronary arteries, severe myocardial hypertrophy, increased work load on the heart, acute diminution of the minute heart volume, acute or sharply pronounced anaemia. In most cases angina pectoris is caused by coronary atherosclerosis and the possibility of other factors to be its only cause is extremely questionable.

Nonetheless, the term 'atherosclerosis of the coronary arteries' cannot be used as a synonym of angina pectoris. The results of comparing the findings of coronarography and the clinical picture point to the existence of painless forms of coronary atherosclerosis and to the possibility of angina pectoris and even myocardial infarction developing in people with anatomically normal coronary arteries.

Pain is the principal symptom of angina pectoris and until quite recently it was presumed to be its only clinical manifestation. At present it is considered permissible to make the diagnosis of angina pectoris from the character of the pain syndrome, but to make the diagnosis more convincing it is necessary to substantiate it with objective findings, e.g. the disclosure of foci of deficient blood supply to the myocardium during an attack, detection of disorders of electrophysiological and metabolic processes in the myocardium, and demonstration of impaired contractibility of its ischaemic areas.

It would seem expedient to distinguish the common (classical) and specific forms of angina pectoris, according to the results of the clinical study of the patient, combined with the findings of instrumental examination. The first form occurs much more frequently than the second. Classical angina pectoris is manifested as single attacks whereas specific angina pectoris usually occurs as a series of attacks following one another at intervals of 5 to 10 minutes. Both variants of angina pectoris had been known as early as in Heberden's time.

In the stable classical form of angina pectoris, pain appears in association with physical effort, emotional stress, the effect of environmental factors or, at times, with no obvious cause. Its intensity may be quite different in various individuals and may even change noticeably with every new attack in the same patient. According to the character of the sensation, this pain may be cutting,

pressing, as if searing the heart, strangling the throat or constricting the chest.

In most cases the pain arises in the thoracic cavity behind the sternum and then spreads in all directions. It arises most often behind the upper part of the sternum than behind the lower part; less frequently it is at first felt close to the sternum, in the epigastrium, in the region of the left shoulder blade or the left arm. The more severe the attacks of pain, the more extensive is the zone of their spread from the primary focus.

Extension of the precardiac pain to the neck, supraclavicular region and upper limbs, to the jaws and sometimes to the teeth is particularly often encountered. The left half of the chest and the left upper limb are affected more frequently than the right. The sensation in the upper limb is often described as numbness and weakness rather than as pain. In rare cases of angina pectoris the pain was referred to the left lumbar region and left part of the abdomen (Moiseyev, 1971) and to the lower limbs.

Much diagnostic significance should be attached to the structure of the pain. In angina pectoris the pain always grows gradually but ceases rapidly. The duration of the period of its intensification is always much longer than the duration of its disappearance.

The severity and duration of the pain vary noticeably in different patients. Without nitroglycerin the pain may last several seconds to half an hour and longer. If nitroglycerin is taken when the pain is growing in intensity it brings complete relief in a few minutes as a rule. Nitroglycerin taken at the peak of pain may prove ineffective. The earlier the drug is given, the sooner it brings relief to the patient.

Preceding generations of physicians distinguished individual forms of angina pectoris according to the conditions of its origin. They called the attack angina pectoris of effort when the attacks of retrosternal pain occurred under the effect of increased work load on the heart, e.g. when climbing the stairs. They also included cases of angina pectoris occurring after a meal or under the effect of smoking, exposure to cold or wind, and emotional stress in this group. Attacks of retrosternal pain unassociated with physical exertion or emotional stress were designated angina pectoris at rest.

For the purposes of differential diagnosis it is expedient to separate classical angina pectoris into **fresh, stable, dysadaptational** and **unstable.** This suggested classification is based on the peculiarties of the clinical course taken by angina pectoris; knowledge of them helps in distinguishing angina pectoris from the intramural and subendocardial forms of myocardial infarction.

Pain is a classical, but not the only symptom of angina pectoris. In many cases it occurs together with nausea, dizziness, general weakness, eructation, heartburn, profuse or local perspiration and

difficult breathing. These symptoms and signs are often attendant to the pain but sometimes appear instead of it. Having made it a rule to ask the patient every time about the factors which cause and relieve pain the physician quite rapidly establishes that these recently developed sensations, just as the classical pain, occur after physical exertion and disappear soon after it is ended, or after taking nitroglycerin.

A more common, though no less perfidious, is another disguise of fresh angina pectoris. Pain first arises not behind the sternum and even not in the precardial region, but on the periphery in the zones to which it is referred. For some time the pains in these zones (the fingers of the left hand, the teeth, the arm) are not accompanied by pain in the heart and are looked upon by the patient as some other affliction (Tetelbaum, 1960). Shortness of breath is a still more frequent and hazardous disguise of angina pectoris. The diagnostic difficulties arise not because of any special perfidy of this form of angina pectoris, but because the patient attributes his sensations to some other cause. He thinks that the constriction he feels on his neck is dyspnoea, which makes him stop any work requiring a certain amount of physical effort. Gallavardin (1924) was evidently the first to pay attention to the association of this painless respiratory block with angina pectoris.

Medical experience shows that in our time too this form of angina pectoris is often thought to be dyspnoea caused by heart failure. When the search for proof of heart failure fails, the patient's complaint is attributed to globus hystericus and this continues until a typical pain syndrome develops in attendance to the 'invisible dyspnoea'.

In some cases angina pectoris is manifested for a lengthy time as sudden episodes of muscle weakness in the left upper limb. This weakness is sometimes attended by a sensation of numbness of the ring and little fingers of the left hand. The cause of this muscle weakness becomes obvious when the episodes coincide in time with attacks of pain in the region of the heart.

Anginal attacks at rest occur mostly at night when the patient is sleeping. He is awakened by a sensation that somebody had prevented him from taking a deep breath, or by pain in the region of the heart. This pain is attended by fear of death and pronounced vegetative reactions (perspiration, the urge to urinate). The intensity and duration of pain in angina pectoris at rest noticeably exceed those of pain in angina pectoris of effort.

The diagnosis of **fresh angina pectoris** is made when the patient has characteristic retrosternal typically referred pain or the clinical disguises described above over a period of several days or weeks. When these sensations occur suddenly and trouble the patient daily, they usually prove to be either the precursor or a manifestation

of acute myocardial infarction. When fresh angina pectoris develops insidiously and the patient is unable to determine when it had begun, the condition usually transforms into stable angina pectoris. If fresh angina terminates in myocardial infarction, the period of time between the origin of the angina and the formation of the infarct is designated 'preinfarction state'.

It is our experience that fresh angina pectoris, particularly in patients with a history of myocardial infarction, usually proves to be a manifestation of new acute myocardial infarction. We think that the diagnosis of fresh angina pectoris may only be established after subendocardial or intramural myocardial infarction has been ruled out.

The stereotypy of attacks is the principal diagnostic sign of **stable angina pectoris.** The character of the pain, its duration, intensity, localization and radiation are practically always the same. In some patients the attacks of pain are mild and the general condition is not disturbed, while in others they leave a feeling of jadedness and mental depression. It is typical that in one and the same patient these attacks are quite comparable in severity. There is no noticeable change in the rate of the heart beat and arterial pressure level during the attacks. The pains grow gradually in the form of intensifying attacks of burning or constriction following one after the other. On reaching their peak, which is always about the same, they quickly disappear. The high efficacy of nitroglycerin in this form of angina pectoris is common knowledge.

Stable angina pectoris is encountered in patients with severe stenosing atherosclerosis of one or all three main coronary arteries. The severity of the attacks is determined neither by the number of arteries nor the degree to which they are affected. The attacks may arise at any time, night or day. The stereotypy of the attacks is of diagnostic significance and not the time of their occurrence.

The concept of stable angina pectoris of effort is based on the assumption that for each patient there is a certain amount of physical effort which, if exceeded, causes a discrepancy between the requirements of the myocardium in oxygen and the capacity of the stenosed coronary artery to an adequate increase in the volumetric rate of blood flow. In other words, a characteristic attack of pain occurs. Clinical study of angina pectoris discloses many cases of the disease which do not fit this scheme. Chernogorov (1954) encountered cases when slow pacing and walking over an even stretch caused attacks sooner than if the patient walked quickly and climbed stairs.

Many of our patients developed anginal attacks immediately after a meal. Some of them preferred going to work without breakfast. The first mouthfuls of food precipitated an attack; consequently we could not attribute the origin of the attack to an increased work

load on the circulatory system. It is general knowledge that an anginal attack often happens when a cold breeze is blowing on the face and ceases when the patient turns his back to the wind.

In some patients attacks of angina pectoris always arise in the morning when they set off to work. The patient stops walking and when the attack ends continues on his way even at a quicker pace. The attacks do not recur although the second work load exceeds the first by far. The specific feature noted is an invariable occurrence in a peculiar form of angina pectoris marked by series of attacks arising at night when the patient is resting. In daytime such patients are sometimes capable of considerable physical exertion which does not induce pain.

Electrocardiography performed after physical exertion provides a possibility for confirming the justness of these clinical findings. One and the same exercise induces an attack of pain and characteristic ECG changes in one test and often fails to cause them in another. The irregular reproduction of the attack and its electrocardiographic equivalent is encountered particularly often in patients with affection of only one coronary artery and is almost not encountered at all in those with affection of the three main coronaries.

The enumerated facts may be explained by linking the origin of angina pectoris not only with coronary atherosclerosis, but with functional disorders of the regulation of coronary circulation. The justness of this conclusion is verified by the possible development of infarction in individuals with anatomically normal coronary arteries. This conclusion will prove very valuable in making the differential diagnosis between this form of angina pectoris, which we have termed **dysadaptational**, and heart neurosis and other forms of cardialgia.

When the usual stereotypy of anginal pain changes in a patient with the stable form, it is said that the condition has developed into **unstable angina pectoris**. The stereotypy of pain changes because of some kind of febrile disease, physical or emotional overstress and at times for no obvious reason. The attacks of pain in such cases become more frequent or severer. The radiation of pain changes noticeably at times, pain is referred to areas in which it had not been experienced before. Sometimes nausea, perspiration, palpitation, and difficult breathing develop in attendance to the old pain. The pain occurs at night, although previously it had only appeared in daytime during physical exertion. In other cases long-existing nocturnal pain is suddenly accompanied by paroxysmal dyspnoea which had formerly never been experienced. Attacks of angina pectoris arise during defaecation or urination.

The change of stable angina pectoris to the unstable form is encountered particularly often in post-infarction patients. Examination of patients with unstable angina reveals that the attack of pain

is attended by an increase in the pulse rate and arterial pressure, and by dyspnoea which is sometimes paroxysmal. The unstable form may last several weeks or months. It may terminate by developing into stable angina, or by the formation of a myocardial infarct. Remission with complete cessation of the attacks of pain sometimes occurs. Unstable angina pectoris should always be regarded as a forerunner or a manifestation of myocardial infarction.

According to the results of coronarography, 30 per cent of patients with unstable angina pectoris had one constricted coronary artery, 30 per cent had two and another 30 per cent had three constricted coronary arteries. In 10 per cent of patients the coronaries were found to be normal. Soviet authors observed about the same incidence of coronary involvement in the stable form of angina pectoris. The pronounced pattern of intercoronary collaterals and the degree of stenosis of the coronary arteries were approximately the same in the groups of patients which were compared.

Without going into the details of what causes angina pectoris we nevertheless should draw attention to the fact that in approximately 10 per cent of patients unstable angina pectoris was consequent upon some other disease rather than upon stenosing coronary atherosclerosis.

Besides the classical forms of angina pectoris that are described a **specific form** (variant) is distinguished. Its clinical picture is characterized by the following features.

1. The attacks of pain usually occur at the same time of night or day, e.g. at sunrise.
2. The specific form of angina pectoris usually occurs not as a single attack, but as a series of two to five attacks of pain in succession. The interval of time between the attacks of a series varies from 2-3 to 10-15 minutes.
3. A patient who has attacks of specific angina pectoris feels well in daytime and may take part in physical work without experiencing any pain.
4. The specific form of angina pectoris differs from the common form in the structure of the attack. The period of intensifying pain in this form is about the same as the period of its disappearance, whereas in ordinary angina pectoris the first period is much longer than the second.
5. The *S-T* segment is elevated above the isoelectric line during the attack of pain, thus pointing to ischaemia not only of the subendocardial but also of the subepicardial coat of the myocardium.

In order to make the diagnosis of angina pectoris, it is evidently necessary to disclose the connection of the pain with coronary insufficiency and not with coronary atherosclerosis. With the accumulation of knowledge in the field of heart physiology many methods for revealing latent coronary insufficiency were suggested and tested

in clinical practice. The method of repeated examination of heart function at rest and during physical effort or emotional stress is the one most widely applied to date. Increased demand is made upon the whole body or the heart alone. Methods for detecting coronary insufficiency without exercises have been recently proposed.

The results of exercise tests are appraised by means of electrocardiography, scintigraphy, echocardiography and electrokymography. The high prevalence of angina pectoris and the doubtful reliability of the clinical methods for its diagnosis justify a more detailed description of the most widely used methods for disclosing coronary insufficiency underlying it.

Foci of deficient blood supply in most cases of ischaemic heart disease are localized in the subendocardial coat of the left ventricle. Oedema of the ischaemic myocardial cells with impairment of their mechanical and bioelectric activity occurs under the effect of ischaemia. These disorders may be detected by tests for the activity of some enzymes in the blood and by ventriculography, echocardiography and electrokymography. All Soviet medical establishments use the method of electrocardiography carried out during or after exercise on a treadmill or a bicycle ergometer. This circumstance explains why the diagnosis of coronary insufficiency by means of this method is described in greater detail.

In 1928 Feil and Siegel observed a patient who developed an attack of angina pectoris during ECG recording. Nitroglycerin relieved the pain completely. ECG were recorded at the beginning, at the peak and after cessation of the attack of pain. The *S-T* segment retained its upsloping direction at the beginning of the attack. Its initial part was below the isoelectric line. At the peak of the attack the *S-T* segment was horizontal and far below the isoelectric line. After cessation of the attack these changes disappeared.

Modern medicine possesses at its disposal the technology required for continuous ECG recording of all anginal attacks occurring within any period of time. Physicians nevertheless prefer testing the condition of the coronary blood flow by the methods of graded exercise which provide for appraising the capacity of the circulatory system to ensure adequate blood supply to the working organs under condition of their functional activity.

Moderate narrowing of the lumen of the coronary arteries usually does not lead to diminished functional capacity of the heart. In marked constriction of arteries blood supply to the heart at rest may remain normal. The greater the physical exertion the more probable the appearance of foci of deficient blood supply to the myocardium, primarily in areas supplied by arteries constricted to the maximum.

Two rivalrous exertion methods are currently applied, namely, exercise on a bicycle ergometer and exercise on a treadmill. On a bicycle ergometer the load may be graded with the patient seated or

lying down. Many patients cannot pedal a bicycle ergometer and can only be examined after special training; on a treadmill the patient can perform graded exercise at the very first examination. The results of the test may be correctly interpreted only by a physician skilled in the method and capable of appraising the effect of cardiac and extracardiac factors on the findings.

Experience accumulated to date allows the exercise test to be considered a safe manipulation which yields very valuable information on the association of the chest pain with the condition of the coronary blood flow. The test must be conducted only under the supervision of a physician trained in the fundamentals of resuscitation. Special attention should be focused at the rate with which the exercise load is increased. The heart beat should reach maximum or submaximum values in about 10-12 minutes. Otherwise fatigue and dyspnoea will make it necessary to stop the test before the desirable heart beat is attained.

The maximum rate of oxygen consumption by a healthy heart is determined by the amount of work it performs. In ischaemic heart disease the consumption of oxygen in the area supplied by the stenosed artery depends, on the one hand, on the amount of the exertion, and on the other, on the degree of blood supply to the myocardial area through the stenosed artery and collaterals. A focus of ischaemia develops during physical effort in the area supplied by the stenosed artery. It is clinically manifested by pain or impaired heart rhythm. When these syndromes develop the test must be discontinued irrespective of the heart beat attained.

If the exercise does not induce marked pain or arrhythmia, the load must be increased quickly until the heart beat reaches a submaximum value, which in the case of middle-aged and old persons is about 110-115 per minute. In a small number of cases with ischaemic heart disease objective signs of coronary insufficiency appear only after maximum exertion. This does not refute the diagnostic value of submaximum exertion, but merely indicates that the positive result of the test confirms the tentative diagnosis of coronary insufficiency, while a negative result does not rule it out.

The collaboration of the physician and the patient is a necessary condition for the correct performance of the exercise test. The patient should be made understand the purpose of the test. It should be pointed out that to arrive at a correct diagnosis the patient should cooperate by working with maximum speed, ignoring fatigue, dyspnoea and pain in the legs. If the patient is encouraged during the test, his ability to tolerate the mounting physical load will be noticeably increased.

Pain deserves special attention on the part of physician and patient. Many patients stop working as soon as they experience the first unpleasant sensations in the chest which may be of extra-

cardiac origin. On repeated examination chest pain in these patients often arises only on submaximum exertion. In all probability the results obtained will be more uniform and comparable if the patient is told to continue the exercise until he feels pain the intensity of which is about as great as that of pain in spontaneous attacks of angina pectoris. The continuous study of the changes in the configuration of the ECG on the oscilloscope makes for better evaluation of pain felt in the region of the heart. Pain of coronary origin is attended by characteristic changes in the ECG, as a rule, and sometimes also by disorders of the rhythm of cardiac activity.

Thus, continuous or graded increase in physical exertion during the test should be perpetuated until the rate of cardiac contractions reaches submaximal level or until the physician stops the test because of marked dyspnoea, dizziness, arrhythmia, disturbed appearance of the patient and his complaints of pain in the heart or because of sharp depression of the *S-T* segment on the ECG occurring separately or simultaneously with pain in the heart. The patient can stop the test at any time he wishes.

The result of the exercise test is assessed on the basis of changes in the ECG recorded prior to, during, and 10-12 minutes after the test. The clinical evaluation of the results must be based on the following premises.

1. Focal myocardial ischaemia in 75-80 per cent of cases with angina pectoris is attended by displacement of the *S-T* segment either above or below the isoelectric line. Ischaemia of the subendocardial myocardial coats leads to depression of the *S-T* segment, whereas ischaemia of all the coats of the left-ventricular wall is accompanied by elevation of the *S-T* segment. Its displacement by no less than 1 mm from the initial level is accepted as a diagnostic sign. In the classical form of angina pectoris, the *S-T* segment is depressed. Its elevation occurs in the specific form of angina pectoris and when the active electrode is placed close to a vast cicatricial field in the myocardium.

2. In focal myocardial ischaemia the *S-T* segment is not only depressed, but changes in configuration. From a slightly concave upsloping tracing it gradually changes to a horizontal or slightly convex downsloping tracing.

3. Depression of the *S-T* segment usually appears during physical exertion and becomes less marked after effort ceases. In some cases it can only be recorded at the end of exertion. In rare cases depression of the *S-T* segment is seen only during exertion. The depression may be detected only by continuous ECG recording throughout the test.

4. Short-term disorders of cardiac rhythm (extrasystole, cardiac fibrillation, atrioventricular block) are noted in 5-10 per cent of patients with ischaemic heart disease. They possess no independent

diagnostic value. The appearance of marked arrhythmia of effort is recognized as an indication that serious disorders have developed in the functional condition of the heart. It is encountered both in angina pectoris and in myocarditis.

5. Isolated depression of the *S-T* junction (the point where the ascending limb of the *S* wave is continuous with the *S-T* segment) may be erroneously interpreted as a sign of ischaemic heart disease only when the gradually upward sloping *S-T* segment returns from the junction to the isoelectric level in more than 0.08 second. It was found that depression of the *S-T* junction is always encountered in a healthy person because it is caused by tachycardia.

6. Disappearance of the *T* wave and its isolated inversion during effort from a positive to a negative, or from a negative to a positive tracing often occur during effort or soon after it in patients with a history of myocardial infarction and in those with atherosclerotic cardiosclerosis. Most contemporary authors attach no diagnostic significance to these signs since they are not only encountered in ischaemic heart disease, but also in many other diseases. In our clinic Lobova and Timofeev encountered these signs (as it turned out later) in patients with chronic myocarditis of toxoplasmic and other aetiology.

7. In approximately 10 per cent of patients with typical clinical manifestations of angina pectoris and sharply pronounced atherosclerosis of the coronary arteries exertion is not attended by the characteristic changes in the *S-T* segment. Even maximum effort induced neither pain in the chest, nor changes in the ECG in some patients who had suffered from myocardial infarction (Kattus, 1974). It proceeds, therefore, that a negative result of the exercise test does not allow the diagnosis of ischaemic heart disease to be excluded.

8. Displacement of the *S-T* segment sometimes precedes pain in classical angina pectoris and is the only indication that myocardial ischaemia is developing at effort in the specific form of angina pectoris and in the asymptomatic form of ischaemic heart disease. Despite the absence of pain, sharp displacement of the *S-T* segment should be regarded as a signal for ending the test.

9. In about one fourth of cases with angina pectoris the characteristic electrocardiographic signs of myocardial ischaemia are demonstrated in any one of the leads. Foci of ischaemia in the anterior and lateral walls of the heart are usually demonstrated in leads V_5 and V_4, while foci in the posterior wall at times only in leads III or aVF. The experience we have gained shows that simultaneous recording in more than one lead may increase the number of objectively confirmed cases of angina pectoris by approximately 4-5 per cent.

In appraising the ECG changes occurring under the effect of

physical exercise, it should be borne in mind that myocardial ischaemia is only one of the causes of segment *S-T* depression. False positive results of the exercise test happen in hyperventilation, neurocirculatory asthenia, and in patients given cardiac glycosides, diuretics, quinidine and novocainamide.

It is particulary difficult to rule out the effect of hyperventilation because more or less marked dyspnoea always develops during the exercise test. To exclude the effect of this factor on the results of the examination Nechaev et al. (1977) recommend performing the hyperventilation test before the exercise test. The results of the exercise test may be regarded positive only if hyperventilation has not given rise to ECG changes characteristic of angina pectoris.

Patients taking cardiac glycosides or diuretics may produce false positive results of the exercise test even when the *S-T* segment on the resting ECG is on the isoelectric line. To exclude the effect of drugs on the results it is advisable to perform the exercise test after they are discontinued and the patient is completely free of their effect.

It is likewise important to take into consideration the position of the electrodes on the chest during the test. If the active electrode is placed over the zone of an extensive scar or on the border between the cicatricial tissue and the undamaged myocardium, the *S-T* segment on the ECG recorded during exercise is often elevated probably because the normal pathways of the spread of depolarization and repolarization processes in the myocardium are disrupted. These factors are also responsible for the considerable difficulties in interpreting the results of the exercise test in patients with the Wolff-Parkinson-White syndrome and with signs of bundle branch block. These difficulties may be partly overcome by using high-frequency electrocardiography. We cannot judge its diagnostic significance for lack of personal experience.

The exercise test with electrocardiographic control makes it possible to detect coronary insufficiency in most cases of ischaemic heart disease. Without denying its high diagnostic significance we would like to point out the circumstance which limits its value: the dependence of the results on the initial ECG pattern and on the drugs commonly used in the treatment of cardiovascular diseases. Some of these shortcomings can be overcome by using other methods in studying heart activity.

In foci of ischaemia the myocardium contracts weakly or cannot contract at all. In the latter case the wall of the ischaemic area of the heart bulges passively during systole. Hypokinesia, akinesia and dyskinesia (paradoxical movements) of the heart wall are distinguished. An attack of angina pectoris is attended by the formation of one or more ischaemic foci. The myocardium in the foci of ischaemia loses its contractile function, whereas the contraction

of the myocardium in adjacent areas is fully preserved. Even compensatory hyperfunction of normal myocardial areas is sometimes registered.

Foci of altered myocardial contraction may be detected by ventriculography or echocardiography. Some haemodynamic values may also be determined by either method. The results of examination by these methods at rest do not allow foci of fresh ischaemia to be distinguished from disorders of myocardial contraction consequent upon a previous infarction.

Ischaemic foci forming in the myocardium during spontaneous or induced anginal attacks may also be disclosed by scintigraphy of the myocardium with radioactive pharmacological preparations of technetium and thallium. According to some authors, spontaneous anginal attacks are attended by accumulation in the myocardium of a 'cloud-like' ^{99m}Tc pyrophosphate uptake which may encompass part or almost all the area of the heart. This uptake was found only in patients with an attack which lasted no less than 3 minutes. The divulged changes remained 6 to 8 hours after the attack. The authors drew attention to the possibility of using this method for retrospective diagnosis of angina pectoris.

At our clinic Sychova, Rylova and Lobzeva conducted electrocardiography and scintigraphy of the myocardium during attacks of angina pectoris induced by submaximum exercise by the method described above. The activity of creatine phosphokinase and MB fraction was determined simultaneously. In addition to the changes described above they found that the electrocardiographic signs of myocardial ischaemia are demonstrated more often and disappear more rapidly than the scintigraphic signs, and that ^{99m}Tc pyrophosphate may sometimes be detected in the myocardium for one or two days after an attack of angina pectoris and after the electrocardiographic and enzymatic signs of its ischaemia have disappeared. In other cases, ^{99m}Tc pyrophosphate uptake by the myocardium was detected only 24 hours after the clinical, electrocardiographic and enzymatic signs of short-term myocardial ischaemia had disappeared but not during the exercise test. Temporary ischaemia of the myocardium in angina pectoris may evidently cause the formation of micronecroses in it in some cases.

The subjective manifestations of angina pectoris are very diverse. Their correct evaluation can only be made when a certain amount of experience and skill is gained in talking with the patient and analysing the results of this conversation, which often consists of many talks. The objective signs of the syndrome are no less diverse. Complex instrumental methods of examination must be resorted to at times to detect them.

The diagnosis of angina pectoris forms the basis for planning a program of non-operative and, whenever necessary, surgical treat-

ment of the patient. The solution of these problems of practical significance primarily calls for the differentiation of angina pectoris from other diseases whose subjective and sometimes objective manifestations to a great degree resemble those of angina pectoris. The classical form of angina pectoris often must be differentiated from non-coronarogenic cardialgia, and the unstable form from microfocal myocardial infarction. It is our experience that diseases of the chest wall are often mistaken for angina pectoris.

Unstable angina pectoris is like a link between the stable form and localized infarct which for some causes usually forms in the subendocardial area of the myocardium. It is sometimes extremely difficult in actual practice to put one's finger on the precise criteria distinguishing ischaemia accompanied by oedema of the ischaemic myocytes from graver ischaemia which had terminated in necrosis of the myocardium. Localized subendocardial infarction, in turn, may be regarded as a precursor or a herald of extensive, often transmural myocardial infarction. The differences between them are only of quantitative character. These quantitative differences between the various forms of ischaemic heart disease unfortunately often cause considerable diagnostic problems the solution of which determines the choice of therapeutic measures.

Pain in localized subendocardial myocardial infarction in some cases in no way differs from pain in unstable angina pectoris. Therefore, to distinguish these forms of ischaemic heart disease the physician must weigh the character of the combination of pain with disturbances in the other functions of the heart; a longer follow-up of the course of the disease and additional laboratory studies are necessary to reveal these disturbances.

The diagnosis of localized intramural or subendocardial infarction may be made when characteristic ECG changes and enzymatic and non-enzymatic signs of myocardial infarction develop in addition to the pain. The ECG changes include depression or elevation of the *S-T* segment, isolated or combined with inversion of the *T* wave. The *Q* wave is not changed. Isolated *T* wave inversion was encountered in two of our cases confirmed on autopsy. The changes listed above are always found in angina pectoris too. Differential diagnostic significance should be attached not to the changes themselves, but to their duration.

The electrocardiographic signs of coronary insufficiency in classical angina pectoris last 5 to 30 minutes after the attack. In unstable angina pectoris they may be detected within 24, rarely 48 hours. In localized intramural or subendocardial infarction they are always found for more than 24 hours, and usually for more than 48 hours.

The activity of the cardiac MB creatine phosphokinase fraction stays normal in anginal attacks uncomplicated by necrosis. In unstable angina pectoris it sometimes exceeds the upper boundary

of its activity in healthy persons by 1.3 to 1.4 times and reaches 11 mME/ml (according to Zhuravleva). Moderate increase in MB-creatine phosphokinase activity persists for no more than 24 hours after a severe anginal attack ceases. In localized intramural or subendocardial infarction its activity increases by more than 1.5 times and stays increased for 2 to 3 days and longer.

The activity of serum enzymes increases briefly in localized myocardial infarction. It cannot be sometimes demonstrated for a variety of reasons. In this type of myocardial infarction there are usually no diagnostically convincing changes on the ECG. Foci of necrosis in such cases may sometimes be detected on scintigrams taken after intravenous injection of technetium pyrophosphate (^{99m}Tc-pyrophosphate) which accumulates in the foci of necrosis or in areas of sharply diminished blood supply to the myocardium. In view of the small size of the necrotic focus Sychova and Rylova at our clinic determine the zone of increased radioactivity not visually but by means of a computer, thus obtaining the best results.

Movshovich (1975) was the first to focus attention on the great differential diagnostic importance of stromal inflammation which always develops in attendance to localized myocardial infarction and is marked by a regular increase of the concentration of chloride-soluble mucoprotein, other protein-carbohydrate complexes, and collagen derivatives in blood. Their increased content is found beginning with the second or third day of the necrosis and lasts for three or four weeks. The content of these substances in blood in the classical and unstable forms of angina pectoris does not change.

Disorders of cardiac contractions, automaticity and other functions are concomitant to pain more often in localized myocardial infarction than in unstable angina pectoris. It is likewise important to bear in mind that pain and necrosis may not be simultaneous. Attacks of angina, paroxysmal dyspnoea and disorders of cardiac rhythm are usually the forerunners of myocardial infarction, but sometimes they are its first clinical manifestations. Repeated performance of the examinations listed above may be of noticeable help in the differential diagnosis between unstable angina pectoris and localized myocardial infarction.

Non-coronarogenic Cardialgia

The very diverse clinical manifestations of coronary insufficiency must be differentiated particularly often from functional diseases of the cardiovascular system, non-coronarogenic cardialgia, and diseases of the aorta, the diagnosis of which usually begins with analysis of the pain experienced in the region of the heart. In some cases this pain predominates in the picture of the disease, while

in others it is its only symptom. This section deals only with the methods for differentiating these diseases from angina pectoris.

Neurocirculatory Dystonia

In the practice of an out-patient clinic there are frequent cases when patients, usually females, have many complaints of disturbances in the function of the heart and other organs, but even the most thorough examination discloses a very small number of objective signs of a disease in them. These patients are usually treated for a long time for 'chronic coronary insufficiency', 'chronic flaccid rheumatic carditis' often combined with 'mitral insufficiency', vegetoneurosis and the diencephalic syndrome.

The vivid and numerous subjective manifestations of the disease are remarkably stable. The most diverse therapeutic measures are often insufficiently effective and cannot relieve the sufferings of such patients. The disease may lead to loss of working capacity, but even in this event it does not result in cardiosclerosis, myocardial infarction or heart failure. The absence of a tendency to advance was one of the reasons why this disease was included in the group of 'functional diseases of the heart'.

Many clinicians regard functional cardiovascular diseases as an example of corticovisceral pathology the most characteristic feature of which is disturbed normal relationship between the central nervous system and the activity of the visceral organs. Some authors call these diseases 'heart neuroses', using this term to mean general neurosis marked by symptoms and signs of disorders mainly of heart activity.

Disturbed higher nervous activity is found only in some cases of functional heart diseases. Savitsky suggested the term 'neurocirculatory dystonia' to designate functional diseases of the heart with no obvious signs of general neurosis, thus emphasizing simultaneous involvement of the nervous and cardiovascular systems. Functional diseases of the heart are also called 'vegetative dysfunction', 'systemic neurosis', 'cardioencephalic syndrome', 'neurocirculatory asthenia', and 'vegetative dysfunction'.

It is believed that functional cardiopathies develop as a reaction of man to the increased frequency and force of stress situations in his life. The clinical manifestations of functional cardiopathies are attributed to hyper-reactivity of either the sympathetic or the sympathetico-adrenal system ensuring adaptation of the cardiovascular system to the conditions of stress.

Functional cardiopathies are a clinical entity which, just as many other syndromes, may be of various aetiology. Their subjective and objective manifestations are rather stereotyped. Diagnostic difficulties usually arise only in the middle-aged and elderly and in

patients suffering from an organic heart disease. Diagnostic errors are mostly made because of the incorrect interpretation of the cause of the pain encountered in all forms of functional cardiopathy. Neurocirculatory dystonia is most commonly mistaken for angina pectoris.

Much effort has gone into comparing the components of the attack of pain in neurocirculatory dystonia and angina pectoris. It was established that short-term pressing and constricting retrosternal pains arise much more frequently in angina pectoris than in neurocirculatory dystonia. Long-term recurrent pain in the region of the heart, which intensifies from time to time, is more typical of neurocirculatory dystonia.

In angina pectoris the pain intensifies gradually, lasts no longer than 30 minutes and quickly disappears. In the specific form of angina, the attacks of pain are of greater intensity and they recur. No pain is felt between attacks. In neurocirculatory dystonia pain intensifies to a high degree and may become very severe. Intensifying and abating in waves, it may persist for several hours and even days resembling the pain in myocardial infarction.

Pain in neurocirculatory dystonia is always attended by frequent and shallow breathing and sometimes by occasional extrasystoles. The development of paraesthesia and sometimes cramps in the fingers and toes is explained by hyperventilation and concomitant alkalosis. Pain referred to the neck in an anginal attack is subjectively perceived by the patient as 'a lump in the throat' which hinders easy breathing. Experience in exercise tests shows that arrhythmias may also appear in angina pectoris. The heart beat rate does not change in angina pectoris, as a rule, but sometimes increases markedly in neurocirculatory dystonia.

The popular belief that trial nitroglycerin therapy possesses considerable differential-diagnostic significance should be regarded as greatly exaggerated. After nitroglycerin pain subsides markedly in most cases of neurocirculatory dystonia, evidently because of the change induced by the drug in the blood supply to the brain. In quite a number of cases of angina pectoris nitroglycerin relieves the pain only in part, but not completely. It should be borne in mind that nitroglycerin tablets kept in an open flask or in a flask plugged with cotton lose their efficacy very rapidly, failing to relieve pain in both angina pectoris and neurocirculatory dystonia. Reference of pain in angina pectoris often coincides with its reference in neurocirculatory dystonia.

The clinical manifestations of pain in neurocirculatory dystonia and angina pectoris are most often of the same pattern and cannot be used as a criterion for differential diagnosis. We think that since practitioners are not sufficiently aware of this, it becomes the cause of common diagnostic error, namely, inability to distinguish angina

pectoris from neurocirculatory dystonia. Analysis of the materials obtained by Fogelson (1956) shows that an unsubstantiated diagnosis of angina pectoris is made in most instances.

Neurocirculatory dystonia differs from angina pectoris in symptoms and signs attendant to the pain. A patient with angina complains of attacks of pain in the region of the heart and usually has neither subjective nor objective signs of ill health in the periods between attacks. A patient with neurocirculatory dystonia is never in sound health. The pain in the heart is often replaced by a vegetovascular crisis marked by shivering, chill, elevated arterial pressure, often with polyuria or diarrhoea. Between attacks the patient complains of headache, increased perspiration, dizziness, muscle weakness, and rapid fatiguability from muscular and mental work. Hyperhidrosis and hyperalgesia in the region of the heart are found on examination. Approximately half the patients have subfebrile body temperature. Impotence or mild deficiency of ovarian hormonal function is often encountered.

The differential diagnostic significance of changes in the heart and its reactions to exercise stem from the following observations. In neurocirculatory dystonia the heart is normal in size and an apical systolic murmur is often heard. The electric axis of the heart is normal. Diphasic or negative *T* waves are often recorded (especially in chest leads) in patients with heart of normal size and in normal position of its electric axis. In angina pectoris, the systolic murmur is at first heard over the aorta. The heart in this period of the disease is still normal in size, but its electric axis is often displaced to the left. In a patient with no history of myocardial infarction, the *T* waves on the ECG are positive. Negative *T* waves are found only in obvious enlargement of the left ventricle. A negative *T* wave in such cases is usually one of the signs of the electrocardiographic syndrome of left-ventricular overstrain. A systolic apical murmur develops in addition to the systolic murmur over the aorta at that time of the disease when enlargement of the left ventricle is clearly demonstrated and the electric axis of the heart is always displaced to the left.

When a patient with ischaemic heart disease and signs of angina pectoris changes from a horizontal to a vertical position, no marked changes occur in the rate of the heart beat or on the ECG. The same movement by a patient with neurocirculatory dystonia will cause an increase in the pulse rate usually by more than 15 per minute, often a depression of the *S-T* segment and deeper negative *T* waves already recorded on the ECG.

In neurocirculatory dystonia negative *T* waves are recorded more frequently in the right chest leads and much less frequently in all other chest leads. In ischaemic heart disease with anginal attacks negative *T* waves appear at first in the left chest leads as a rule.

The prescription of beta-adrenergic receptor blocking agents, potassium salts and Valsalva's manoeuvre in neurocirculatory dystonia are often attended by the change of negative *T* waves to positive. In ischaemic disease with attacks of angina pectoris these measures induce the change of negative *T* waves to positive in only very rare cases. Some authors point out that negative *T* waves in neurocirculatory dystonia sometimes change to positive with no apparent cause. We think that such changes in the *T* wave are encountered much more frequently in ischaemic heart disease.

Exercise with electrocardiographic control often allows neurocirculatory dystonia to be differentiated from ischaemic heart disease which is attended by anginal attacks.

As it is underscored above, ECGs recorded when a patient with neurocirculatory dystonia is in a horizontal and vertical position noticeably differ in the rate of cardiac contractions, position of the *S-T* segment, and shape of the *T* wave; this is not encountered in ischaemic heart disease with attacks of angina pectoris.

Depression of the *S-T* segment is noted during the first seconds of the exercise in patients with neurocirculatory dystonia. The continuation of the exercise, even with increase to submaximum load, is paralleled by a return of the *S-T* segment to the isoelectric line. A typical attack of angina pectoris never develops either during the return of the *S-T* segment to the isoelectric line, or during the later stages of the test. This order of ECG changes during exercise is sometimes also encountered in patients who have no signs of neurocirculatory dystonia.

Depression of the *S-T* segment during the first seconds of the exercise never occurs in patients with angina pectoris. An increase in the load is attended by a deeper depression of the *S-T* segment and the appearance of typical pains in the chest.

In appraising the results of the exercise test due consideration should be given to the fact that disorders in the regulation of the cardiovascular system characteristic of both neurocirculatory dystonia and ischaemic heart disease may exist in a patient. We would only like to draw the reader's attention to the fact that the reaction to the exercise test of patients with ischaemic heart disease differs from the reaction of patients with neurocirculatory dystonia.

It is easy to distinguish neurocirculatory dystonia from ischaemic heart disease attended by anginal attacks in young patients. The older the patient the more difficult it is to differentiate these two diseases. Information on the course of the disease in the given period of time acquires considerable diagnostic value in such cases. Angina pectoris takes a wave-like course, but nevertheless tends to advance. A patient with ischaemic heart disease develops signs of atherosclerotic cardiosclerosis and its consequences with time. Neurocirculatory dystonia usually begins in young or middle age and in many

years of its existence never results in cardiosclerosis, myocardial infarction or heart failure.

The arguments based on the grounds of long-term surveillance of the course of the disease seem most convincing to us, but the physician, unfortunately, does not always possess such data at his disposal and cannot always await their appearance. Coronary arteriography is recommended when the diagnosis must be established immediately. The lumen of the coronary arteries is constricted by at least half in ischaemic heart disease with anginal attacks, but remains unobstructed in neurocirculatory dystonia.

Climacteric Cardiopathy

In 1874 Kirsch set climacteric cardiopathy apart as a special clinical entity. The condition prevails among females in the period of diminution of ovarian hormonal activity. A reduction of the testicular hormonal activity is usually attended by less marked vasomotor disorders and only in rare cases it leads to attacks of sharp pain in the region of the heart. Three main syndromes are distinguished in the clinical picture of climacteric cardiopathy: vasomotor, cardiac syndromes and vegetative crises with diencephalic shades.

The vasomotor syndrome in climacteric cardiopathy is manifested in hot flushes, i.e. a sudden sensation of heat in the upper chest, face, head and neck. This sensation is first followed by hyperaemia in these areas and then by sweating. The hot flushes in the various body areas are attended by paraesthesia from time to time (numbness, prickling and formication).

Vegetative crises usually begin with a feeling of cold in the limbs, which is replaced by a sensation of a general chill and shivering of the trunk and limb muscles. In most cases the attacks are marked by prevalence of the tone of the sympathetic nervous system which is manifested by a frequent pulse, paleness of skin, and elevation of arterial pressure. General weakness and often profuse sweating appear at the end of the attack. Severe and protracted pain in the region of the heart sometimes arises during the attack and does not respond to vasodilators and only mildly abates after administration of narcotics. In most cases, however, pain is moderate. Intensifying and diminishing in waves, the pain in the heart persists for many hours and even days. In localization and irradiation it may coincide with pain in angina pectoris.

The intensity of pain is determined neither by physical exertion nor by time of day. Patients often explain the appearance or intensification of pain by emotional stress but interrogation of the patient reveals that the association of emotion with pain is unclear in most instances. Body temperature is often slightly elevated.

Pain in climacteric cardiopathy, just as pain in neurocirculatory dystonia, is often combined with disorders of electrophysiological processes in the heart. Vorobyova and Shishkova (1973) encountered a negative *T* wave in 90 per cent of cases of this disease. In the remaining instances it was depressed or isoelectric. The shape of the *T* wave was not constant during long-term observation over the patient. Its changes were associated with phases of the menstrual cycle rather than with severity of pain. Mild (by no more than 1 mm) displacement of the *S-T* segment was found in 14 per cent of cases. *S-T* depression was more frequent, though its elevation was encountered in rare cases. Combination of pain with *S-T* displacement, *T* wave inversion and, sometimes with disorders of the heart rhythm, often makes it necessary to differentiate climacteric cardiopathy from microfocal myocardial infarction.

After medication with inderal, ergotamine and potassium preparations, the ECG is often normalized (i.e. takes a pattern characteristic of neurocirculatory dystonia). Inversion of a negative *T* wave to positive also occurred under the effect of other factors, for instance after the prescription of sex hormones, and spontaneously as the result of the change of one menstrual cycle phase to another.

Climacteric cardiopathy resembles neurocirculatory dystonia in many respects in clinical manifestation and the results of special laboratory tests but differs from it in the age of the patients. Neurocirculatory dystonia prevails among the young and middle-aged, whereas climacteric cardiopathy is mainly encountered in the middle-aged and elderly. The different age composition of the patients gives rise to new diagnostic problems. Neurocirculatory dystonia has to be differentiated more often from angina pectoris and inflammatory diseases of the heart, while climacteric cardiopathy, in contrast, must be distinguished from myocardial infarction.

Climacteric cardiopathy may set in abruptly or gradually. Myocardial infarction is usually suspected when the disease occurs suddenly with a vegetative crisis. Severe pain suddenly appears in the region of the heart in a person who, to all appearances, is in sound health. The pain is attended by other symptoms of climacteric: chill, hot flushes, profuse sweating, palpitation. The ECG recorded at this moment demonstrates changes in the *ST-T* complex. Subfebrile body temperature and disorders of the heart rhythm develop in addition in some cases. With due consideration for the patient's age the possibility of myocardial infarction seems quite substantiated.

The differential diagnosis between climacteric cardiopathy and myocardial infarction presents no difficulty. In questioning the patient about the subjective manifestations of the disease, the physician spares no effort to detect before all else some details characterising the pain. Whatever the diversity of the clinical mani-

festations of pain in myocardial infarction, it is nonetheless felt for just a few hours in uncomplicated cases. Protracted, unbearable pain occurs only in extensive infarction complicated by pericarditis.

Very intensive pain in climacteric cardiopathy is usually experienced for several hours or days without causing collapse, marked disturbances in the rhythm or other functions of the heart. The discrepancy between the intensity and duration of the pain and the satisfactory condition of circulation is characteristic of climacteric cardiopathy, but is not encountered in extensive myocardial infarction.

Pain in microfocal myocardial infarction varies considerably in intensity from case to case, but it never lasts for many hours or days. After necrosis develops, the pain disappears. It may recur but in such an event it will be a new or recurrent myocardial infarction attended by disturbed activity of the cardiovascular system and by other manifestations of necrosis of the heart muscle. Protracted pain in climacteric cardiopathy does not lead to myocardial necrosis.

Myocardial infarction is marked by increased activity of blood enzymes. The activity of creatine phosphokinase and its cardiac fraction increases on the first day. Increased activity of aspartate aminotransferase (AsAT), lactic dehydrogenase (LDH), and other blood enzymes is encountered from the end of the first or second day. It is necessary to test their concentration in the blood serum because this is of invaluble assistance in judging both the formation and the extent of the infarct. In climacteric cardiopathy blood enzyme activity does not change.

The myocardial area involved in the infarction loses its contractility and bulges out during the systole. In climacteric cardiopathy the capacity of the myocardium to contract during the systole is not impaired. Dyskinesia of the part of the heart muscle that had suffered infarction may be detected by echocardiography. Besides revealing zones of dyskinesia, akinesia and hypokinesia, this method provides information simultaneously about myocardial contraction according to the systolic output and the volume of residual blood in the heart cavity at the end of systole. Marked disorder of heart contractility is evidence against climacteric cardiopathy.

The muscle area involved in the infarction is identified on the echocardiogram by loss of mobility or by paradoxical mobility as compared to that of areas of healthy heart muscle during systole and diastole. In climacteric cardiopathy the echocardiogram is normal.

The increase in the concentration of blood protein-carbohydrate complexes characteristic of myocardial infarction begins after the third day of the disease. Depending on the extent of the infarct and the patient's reactivity this concentration reaches maximum

on the second or third week of the disease exceeding the initial level two- to threefold. At the same time as the metabolism of the protein-carbohydrate complexes in the heart increases, intensified production of collagen begins whose metabolites are found in the blood and urine in ever increasing amounts. Peaks of collagen metabolites testifying to the complete or almost complete formation of the cicatricial connective tissue appear at the end of the third or fourth week of microfocal infarction. In climacteric cardiopathy, the metabolism of protein carbohydrate complexes and collagen does not change.

The results of electrocardiography are of no less differential diagnostic significance. In myocardial infarction the *S-T* segment and the *T* wave in the same lead are displaced in opposite directions. In some cases of myocardial infarction the convex and elevated *S-T* segment is continuous with a sharp negative *T* wave, in others the depressed *S-T* segment is continuous with a giant positive *T* wave. In myocardial infarction the *T* wave grows in size at first and, having reached maximum, gradually becomes smaller. In typical cases of climacteric cardiopathy the slightly depressed *S-T* segment is continuous with a negative *T* wave. Depression of the *S-T* segment, and in rare cases its elevation, are mildly pronounced. The regular changes in the size of the *T* wave characteristic of myocardial infarction are not found in climacteric cardiopathy.

The general body reaction to necrosis also helps in some cases to distinguish myocardial infarction from climacteric cardiopathy. Marked increase in body temperature is a rather frequent occurrence in myocardial infarction but never occurs in climacteric cardiopathy. A short-term subfebrile temperature may be observed in both diseases, but in these cases they may be distinguished by the character of changes in the leucocyte count and ESR. The erythrocyte sedimentation rate is usually normal on the first day of myocardial infarction and increases later. The leucocyte count is ordinarily increased in the first days, but becomes normal in the later stages. These regular changes in the leucocyte count and ESR are only encountered in myocardial infarction.

On summing up the abovestated, the principal differential diagnostic premise may be formulated in the following way: even brief and mild pain in ischaemic heart disease may be a manifestation of myocardial infarction; even very intensive and protracted pain in climacteric cardiopathy does not lead to myocardial infarction. This difference is explained by the dissimilar mechanisms underlying the origin of pain in these diseases.

A patient with climacteric cardiopathy experiences moderate pain in the region of the heart. When this pain arises only from time to time, it has to be differentiated from pain in angina pectoris and cervical osteochondrosis; when the attacks of pain follow in succes-

sion the condition must be differentiated from ischaemic heart disease with threatening myocardial infarction.

A detailed interrogation about the character of the painful sensations, their duration, irradiation, and association with effort and emotional stress provides an idea, in most cases, of the patient's personality and the degree to which his complaints correspond with the clinical picture of typical angina pectoris. The pain in climacteric cardiopathy is distinguished in most cases from the pain in angina pectoris not as much by its different manifestations as by the general impression gained of the picture of the suffering and of the patient himself, which shapes as a result of the talk. The physician's work in such instances resembles that of an artist restoring a work of art; just as mosaic work, the physician must put together the picture of a disease well known to him, but as yet unidentified. Many experienced physicians are highly skilled in this art and claim that no instrumental examination is required for establishing the diagnosis of angina pectoris.

The diagnosis of angina pectoris based on the results of interrogating the patient is confirmed in many cases, but it should nevertheless be borne in mind that the more obvious, though less hazardous, symptoms of climacteric cardiopathy in some middle-aged and elderly patients may overshadow the lesser noticeable subjective manifestations of angina pectoris. Special methods of examination should be resorted to in such instances to rule out angina pectoris. The exercise test with electrocardiographic control is the safest of them. Its results often make it possible to detect signs of coronary insufficiency which may be decisive in substantiating the diagnosis.

Mitral Valve Prolapse

The diminution of the mitral valve fibrous ring during systole ensures complete closure of the atrioventricular orifice in a healthy person, while contraction of the papillary muscles prevents billowing or prolapse of the mitral valve cusps into the cavity of the left atrium. Convincing evidence has been collected in recent years permitting billowing and prolapse of the mitral valve to be distinguished as a clinical syndrome the symptoms and signs of which develop because of impaired mechanisms of coordinated activity of the mitral valve fibrous ring and cusps combined with disturbances in heart excitation, conduction and contraction which have not been fully comprehended as yet.

In 1887 Cuffer and Barbillon were the first to describe additional heart sounds heard in mid-systole. The resulting cadence of heart sound was called 'systolic gallop'. For a long time the systolic

gallop of the heart was considered a purely auscultative phenomenon caused either by separation of the vascular component from the first sound, or by stretching of pleuropericardial adhesions. Even in special manuals on phonocardiography (Böhme, 1972), the origin of additional systolic sounds is explained by stretching of the pleuropericardial adhesions.

The hypothesis of the extracardiac origin of the additional systolic sounds was first advanced by Gallavardin (1913) who heard them in four patients in whom pleuropericardial adhesions were found on autopsy. This was later confirmed by other authors and the belief that additional systolic sounds were not associated with organic heart diseases was generally accepted in cardiology. It was considered most important to distinguish the systolic gallop rhythm which is of innocent origin from the prognostically graver diastolic gallop rhythms (Leatham, 1975) one of which was given the poetic description of 'a cry for help made by the weakened heart'.

Additional systolic sounds are heard alone or in combination with murmurs which are usually arranged in the middle or end of systole but sometimes occupy entire systole. Ventriculography, echocardiography and intracardiac phonocardiography reveal in all such cases signs of mitral insufficiency which are usually mildly pronounced. Cases of mitral valve prolapse with a picture of severe mitral insufficiency, enlarged left atrium and marked hypertrophy of the left ventricle have been described in the recent decade (Pocock and Barlow, 1971).

The fact that the mitral valve prolapse syndrome is diagnosed in young children and infants points to the possibility of its congenital origin. The frequent combination of this syndrome with other congenital heart diseases is also evidence of this. Mitral valve prolapse is often encountered in myxomatous degeneration of the valve ('dangling mitral valve') and in Marfan's syndrome. Prolapse of the mitral valve after injury and in association with rheumatic valvulitis and sclerosis of the heart papillary muscles has been described to date. The accumulated information suggests that billowing and prolapse of the mitral valve cusps should be considered not as a particular disease, but as a syndrome which may vary in aetiology.

Contemporary methods of examination made it possible to obtain a more accurate clinical picture of billowing or prolapse of the mitral valve cusps. Approximately 8-10 per cent of patients who were examined had no complaints. It may be regarded that the disease was asymptomatic. About 85 per cent of patients complained of pain in the region of the heart which was often combined with palpitation. The remaining patients had disorders of heart rhythm unassociated with pain.

Pressing or burning pain is usually felt in the third or fourth in-

tercostal space to the left of the sternum. Much less frequently it is experienced behind the sternum or the xiphoid process. Mild pain persists for hours in most patients and intensifies markedly under the effect of physical exertion or emotional stress. Nitroglycerin relieves the pain completely in some patients, but proves ineffective in others. When intensified, the pain spreads over the entire region of the heart.

Palpitation and intermission in cardiac activity constitute the second complaint in frequency in patients with mitral valve prolapse. Atrial or ventricular extrasystoles, grade I-II delay of atrioventricular conduction, and cardiac fibrillation are frequent findings. Attacks of ventricular tachycardia and intermittent or permanent bundle branch block occur in rare cases. Brief loss of consciousness, a frequent complaint of patients with prolapse of the mitral valve, as well as sudden death are possibly linked with attacks of arrhythmia.

The size of the left ventricle and the shape of the heart are determined by the degree of mitral insufficiency. The size of the left ventricle and left atrium remains normal if only billowing of the mitral valve cusp occurs during the systole. They are enlarged only in patients with conspicuous prolapse of the cusp into the left atrium.

In most cases with this syndrome two heart sounds, the first and second, are heard. The additional systolic sound may occupy the beginning of systole, or it may be closer to its middle or end. If it is recorded within 0.08 second after the first sound, it is designated 'early systolic click', if it is heard in the last third of systole it is called 'late systolic click'. More than half the clicks occupy the middle of systole and are called midsystolic. One and the same patient may sometimes have several additional systolic sounds, e.g. midsystolic and early systolic, midsystolic and late systolic. A third and fourth heart sounds are sometimes recorded at the same time as the systolic clicks.

The additional systolic sound occurring in billowing or prolapse of the mitral valve cusp is distinguished by musicality and a peculiar timbre, which makes it possible to differentiate it from the lower pitched first and second heart sounds. The systolic murmur following it occupies the last part of the systole and is called the late systolic murmur. The early systolic click is followed by a murmur which begins in the midsystole. Pansystolic murmurs are recorded in rare instances. The systolic gallop rhythm comprises the first and a higher pitched additional sounds; it is followed by a short late systolic murmur terminating in the second sound which is perceived (at least we perceive it as such) as an echo of the additional sound. The systolic murmur occurring in prolapse of the posterior cusp of the valve is transmitted to the aorta; it is sometimes attended by a systolic thrill.

Marked depression of the *S-T* segment in combination with wave *T* inversion is encountered in approximately 50 per cent of cases with mitral valve prolapse. Deep and broad *Q* waves are recorded in rare cases. These ECG changes in combination with disorders of excitability and conduction indicate that billowing and prolapse of the mitral valve are very often combined with affection of the myocardium. Segmental analysis of heart contraction by echocardiography demonstrates asynergy of the systole, while ventriculography also discloses asynergy of the diastole in most cases with the syndrome.

The attacks of intensified pain in the region of the heart in combination with the abovedescribed ECG changes and disorders of cardiac rhythm in young patients are often erroneously interpreted as signs of some inflammatory heart disease; in middle-aged and elderly patients they are mistaken for symptoms of ishaemic heart disease complicated by angina pectoris or myocardial infarction.

Mitral valve prolapse is a chronic heart disease. In distinction from myocardial infarction the anginal attack in this disease is not attended by leucocytosis or increased ESR, body temperature stays normal and the dynamic changes in the *S-T* segment and *T* wave characteristic of myocardial infarction are not recorded. The content of enzymes and protein-carbohydrate complexes in the blood is normal even in recurrent attacks of pain.

It is far more difficult to differentiate mitral valve prolapse from atherosclerotic cardiosclerosis attended by attacks of angina pectoris. The subjective manifestations of both diseases may be identical. In some cases the differential diagnosis is made easier by information concerning the onset of the disease. Mitral valve prolapse begins from childhood in many cases. These two diseases differ in the findings of auscultation and phonocardiography. The coronary arteries even in elderly patients with prolapse of the mitral valve are not obstructed, whereas in patients with atherosclerotic cardiosclerosis marked by attacks of angina pectoris their lumen is narrowed by more than half. These differential diagnostic signs are demonstrated by coronary arteriography. In cases with no cardiac fibrillation, left atrial enlargement is a weighty argument in favour of mitral valve prolapse. In doubtful cases the diagnosis is established from the results of echocardiography and ventriculography which record prolapse of the mitral valve cusp.

Myocarditis and Cardiomyopathy

Pain in the region of the heart is the most frequent and one of the earliest symptoms of myocarditis. In most cases it is felt as retrosternal pressure though it may be of an aching, stabbing or

constricting character. Its intensity ranges from weak to unbearable. The pain is of long duration, as a rule; its appearance is not linked with exercise. The pain is referred to the left hand, arm, and shoulder blade. Myocarditis marked by severe pain must be differentiated from angina pectoris, myocardial infarction, neurocirculatory dystonia, climacteric cardiopathy, pericarditis, rheumatic carditis, cardiomyopathy, rheumatic heart disease, and some other diseases. Soviet medicine distinguishes myocarditis unassociated with infection (e.g. serum, drug myocarditis) and infectious myocarditis arising during some infectious disease (e.g. influenza) or soon after recovery from it. The first group of myocarditis is designated primary by Yurenev and Semenovich (1972) and toxicoallergic by Kedrov (1963). The second group is called 'secondary' and 'infectious allergic', respectively.

The symptoms and signs of myocarditis do not depend on its cause. Irrespective of whether or not myocarditis had developed under the toxic effect of some drug, during or after an infectious disease, it is always attended by disturbed heart automatism, conduction and contraction. Cases with myocarditis differ in the severity of the body's general reaction to the disease of the heart and in the severity of the affection of its separate functions. These differences are purely quantitative and their recording is of prognostic rather than of differential diagnostic significance.

In particularly severe myocarditis, the inflammatory process progresses irresistibly causing the patient's death. Mild myocarditis may be asymptomatic and disappear soon after the action of the factor causing it ceases. Much less frequently myocarditis that is at first mild acquires a protracted course and leads to the development of cardiosclerosis and progressive disorders of cardiac activity.

Besides myocarditis, the causes of which are known, there may be forms of this disease the aetiology of which has not been identified. Since the turn of the century an inflammatory process in the myocardium of unknown aetiology is called 'idiopathic myocarditis'. Some of its forms are so much like angina pectoris and myocardial infarction in the intensity of pain, the ECG changes, and the character of affection of heart contraction, that they are often designated 'coronaromyocarditis' or 'pseudocoronary form of myocarditis'.

The pain form of myocarditis is, in most cases, recognized at the patient's bedside. Detailed questioning of the patient reveals all the shades of pain sensation which are of great differential diagnostic value.

Pain in angina pectoris is short-lived. Attacks of the most severe specific form of angina last only 15 to 20 minutes. Sometimes they follow one another in the series but between the attacks of these series there are always intervals during which the patient has no

unpleasant sensations. Pain in myocarditis is distinguished by long duration; it is usually felt for hours and even days. In the acute period of the disease the pain subsides now and then without disappearing completely. The principal difference between pain in these two diseases may be formulated by the following rule: a patient with myocarditis is always aware of his heart, whereas a patient with angina pectoris is not reminded of it at times. This rule is also true of cases with frequent pain attacks encountered in unstable angina pectoris. In our opinion other features of pain are of far less differential diagnostic significance.

The differential diagnostic importance of age is also obvious because the probability of atherosclerosis increases noticeably with age, while myocarditis prevails among the young and middle-aged. Long-existing angina pectoris, a history of myocardial infarction, cerebral circulatory disorders, and high arterial pressure although not proof of ischaemic heart disease, nonetheless serve as weighty arguments in favour of it. In typical cases myocarditis sets in soon after recovery from an infectious disease. Body temperature rises to 38-39°C and stays at this level one to three days. After this, subfebrile temperature is maintained for a period the duration of which varies noticeably. More or less pronounced unpleasant sensations or even pain in the region of the heart and often disturbances in its activity develop in this period.

Subfebrile fever is revealed in 58 per cent of in-patients with myocarditis. Thorough questioning of patients with myocarditis and normal body temperature discloses, in some cases, that they had had fever for one day at the onset of the disease. In angina pectoris body temperature is always normal. The leucocyte count and the ESR are also always normal, whereas in 44 per cent of cases with myocarditis leucocytosis and increased ESR are encountered, in 20 per cent leucopenia and in 16 per cent of cases moderate anaemia are found (Yurenev and Semenovich, 1972). Careful taking of body temperature and clinical blood tests are therefore of very high differential diagnostic value.

Even in long-existing angina pectoris the size and shape of the heart may be normal. With the development of atherosclerotic cardiosclerosis, and particularly in ischaemic heart disease attended by arterial hypertension, the left ventricle becomes enlarged. Signs of left-ventricular hypertrophy and sometimes dilatation are found only in patients with angina pectoris who had suffered myocardial infarction in the past. Soon after the onset of myocarditis, the heart is noticeably enlarged, its contour is smoothed out, and the amplitude of contractions reduces. The pronounced character of these changes is proportional to the severity of myocarditis. In distinction from ischaemic heart disease, myocarditis is characterized by the simultaneous enlargement of the left and right ventricles.

Thus, in ischaemic heart disease with anginal attacks the heart is enlarged at the cost of the left ventricle, whereas in myocarditis it is enlarged because of enlargement of both ventricles. The contour of the heart and the amplitude of cardiac contractions are normal in angina pectoris but undergo marked changes in myocarditis. The characteristic signs of myocarditis listed appear soon after its onset. Signs characteristic of angina pectoris are demonstrated only in patients with pronounced atherosclerotic cardiosclerosis. The differential diagnosis between these two diseases is much easier when the time of the appearance of these signs is recorded.

The heart sounds in angina pectoris are usually distinctly audible, i.e. loud and clear. The systolic murmur is often heard in elderly patients and may also be audible in middle-aged patients with hypertensive disease. In approximately 50 per cent of patients with myocarditis the heart sounds become dull soon after the disease develops. Diminution of the first sound is particularly noticeable. Systolic murmur and gallop rhythm appear only in severe myocarditis, whose clinical picture differs sharply from that of angina pectoris.

Most forms of myocarditis are attended by impaired heart automatism manifested mostly by sinus tachycardia and less frequently by sinus bradycardia. Extrasystoles and delayed atrioventricular and intraventricular conduction are much rarer occurrences. In some cases of chronic myocarditis the elevated and convex *S-T* segment is continuous with a negative *T* wave. Together with a distorted *QRS* complex this produces a picture resembling that of cicatricial changes in the myocardium. Analysis of the features of the pain and the objective signs of the disease which are indicated above permits the physician to differentiate myocarditis from atherosclerotic cardiosclerosis with frequent anginal attacks in most cases.

The clinical picture of chronic myocarditis comprises a series of exacerbations occurring at indefinite periods of time. Each exacerbation is at first usually mistaken for an acute respiratory infection and only the subsequent disorders in cardiac function allow the true cause of the fever to be identified. The clinical manifestations of neurocirculatory dystonia are usually also exacerbated after infection of the upper respiratory tract. According to Istamanova (1958), about 40 per cent of these patients are given long-term but ineffective treatment for myocarditis, rheumatic carditis, and coronary disease.

The high frequency of primarily erroneous diagnosis is explained not only by the similarity of many symptoms and signs of myocarditis and neurocirculatory dystonia, but by the fact that both diseases have no constant signs. Pain in the region of the heart, the periods of more or less long-term subfebrile fever, disorders of heart automaticity, and the systolic murmur occur in both diseases with

approximately the same frequency and the differential diagnosis should therefore be mainly based on the ability to reveal and appraise the shades of the same symptoms and signs. It is common knowledge that such ability is only attained by long habit and experience.

Most patients with myocarditis, neurocirculatory dystonia, and climacteric cardiopathy complain of pain in the heart. In the last two diseases it is always the main complaint, whereas in myocarditis it is usually one of several complaints. In rare cases pain predominates in the clinical picture of myocarditis, but such forms of the disease usually take an acute course and must be defferentiated from angina pectoris and myocardial infarction, and not from functional cardiopathy.

Pain in myocarditis is often attended by disorders of heart automaticity manifested either as sinus tachycardia or sinus bradycardia. Pain in neurocirculatory dystonia may be attended by tachycardia but bradycardia is not encountered. Sinus node automaticity is ordinarily not changed in climacteric cardiopathy. Vegetovascular crises combined with sharp exacerbation of pain in the region of the heart are among the most characteristic manifestations of neurocirculatory dystonia and climacteric cardiopathy. These crises are often erroneously thought to be of diencephalic origin, but examination of the patient reveals no neurological signs of the diencephalic syndrome. Vegetovascular crises are not encountered in myocarditis.

Patients suffering from functional cardiopathy often complain of dyspnoea arising at rest and manifested by shallow breathing interrupted by deep inspiration. A distracting talk leads to the disappearance of tachypnoea and the paraesthesia, visual disorders, and occasionally impaired consciousness caused by it. Troubled breathing in myocarditis usually occurs suddenly, mostly at night. Depending on the severity of the inflammatory process, either paroxysmal dyspnoea or pulmonary oedema develops.

The size of the whole heart or its parts does not change in functional cardiopathy. In more or less pronounced myocarditis the heart is enlarged, its waist is smoothed out. An enlarged heart does not necessarily indicate the presence of myocarditis, but almost always rules out the diagnosis of functional cardiopathy.

Diminution of heart sounds is encountered in most cases of myocarditis but is not characteristic of functional cardiopathy.

Triple heart rhythm in myocarditis differs from that in functional cardiopathy in the frequency composition. An additional heart sound recorded (on the phonocardiogram) on the auscultative and on the high-frequency filter is appraised as an abnormal gallop rhythm, i.e. a sign of myocarditis. In severe myocarditis a short mid-diastolic murmur attendant to the third heart sound (and at times muffling it) is heard. When comparing the findings of repeated

auscultation or repeatedly recorded phonocardiograms it should be borne in mind that any change in the frequency composition, phase and duration of the murmur is a weighty argument in favour of myocarditis.

An inflammatory process in the myocardium is often attended by disorders of heart automaticity, conduction and contractions. The results of long-term observations carried on by Khanina and Shirinskaya show that even in severe functional cardiopathy with frequent 'heart attacks' only myocardial automaticity is disturbed; the function of the heart conduction system and heart contractility undergo no changes. Disorders of atrioventricular and especially intraventricular conduction should be evaluated as very positive evidence in favour of myocarditis. Bundle branch block or arborization block may be encountered only in neurocirculatory dystonia attendant to some organic heart disease.

Vorobyev and Shishkova (1973) encountered stable delay of atrioventricular conduction and transient bundle branch block in a few cases of climacteric cardiopathy. The elderly age of these patients does not allow the association of this disorder with atherosclerosis of the coronary arteries to be ruled out. Disorders of heart conduction develop naturally in the acute period of myocarditis, but become less pronounced with the abatement of the inflammatory process. In the period of remission they may disappear completely. The diversity and the dynamics of changes of conduction during the disease are characteristic signs of myocarditis.

In myocarditis and functional cardiopathy pain in the region of the heart is often accompanied by elevation of body temperature, usually to subfebrile levels. Subfebrile temperature is encountered more frequently in neurocirculatory dystonia and no less frequently in climacteric cardiopathy than in myocarditis. In myocarditis, fever is often attended by leucocytosis and disorders of heart conduction in which case myocardial contraction is often impaired. This is manifested clinically by attacks of dyspnoea or pulmonary oedema. Biventricular heart failure develops in still severer cases. Subfebrile fever is not accompanied by leucocytosis in functional cardiopathy. This disease may lead to loss of working capacity but never to heart failure even if it takes a protracted and severe course.

Thus, in myocarditis pain is often combined with leucocytosis and subfebrile temperature. In more or less long-term myocarditis these are accompanied by the above described changes in the size and shape of the heart indicating weakening of its contractions, and by diverse disorders of conduction and automaticity. Fairly long, severe myocarditis leads to the development of heart failure. Functional cardiopathy is also often accompanied by subfebrile temperature, but even if the disease exists for a long time it is never complicated by heart failure and never leads to cardiosclerosis.

Rheumatic Carditis

In rheumatic carditis pain in the region of the heart is often attended by extracardiac manifestations of rheumatic fever: fever, arthralgia and affection of the central nervous system. The clinical picture of rheumatic fever is composed of a variety of functional disorders of the cardiovascular and other body systems. Neurocirculatory dystonia is mistaken for rheumatic fever more frequently than any other disease not only because the pain is so much like that in rheumatic fever, but also because its clinical picture also consists of functional cardiovascular disorders which sometimes develop together with arthralgia, focal infection, and moderate fever.

The endocardium is affected in rheumatic fever much less frequently than the myocardium. Practical medicine requires that involvement of the endocardium in the inflammatory process is diagnosed as early as possible so that measures can be applied to prevent the development of a heart disease. This is a very difficult diagnostic problem because the symptoms of endocarditis are insufficiently demonstrated and because the information provided by the medical history is of limited value.

The experience of several generations of physicians clearly indicates that it is often very difficult, and at times even impossible, to make the diagnosis of rheumatic endocarditis. It is well known that even the most thorough taking of the medical history of many patients with rheumatic heart diseases does not reveal information on rheumatic fever suffered in the past. Objective examination often discloses chronic tonsillitis and other foci of infection, which are no less frequent in neurocirculatory dystonia than in rheumatic fever.

A substantiated diagnosis of primary rheumatic endocarditis can only be made when signs of a valvular heart disease are detected in the patient. In the initial stage of the disease, however, inflammation of the endocardium merely leads to changes in the conditions of the blood flow through the affected valve. The diagnostic errors occur in this period because it is difficult to distinguish the murmur caused by endocarditis from murmurs arising in myocarditis and from functional murmurs often audible in children and adolescents.

Rheumatic endocarditis is always attended by myocarditis and sometimes also by pericarditis. Proper appraisal of the signs of involvement of these cardiac membranes may make the diagnosis of endocarditis considerably easier.

A diminished first heart sound has long been considered a characteristic diagnostic sign of rheumatic carditis. It should be accepted as an indirect sign of endocarditis if there are no clinical signs

of heart failure, but loses its diagnostic value in patients with symptoms of heart failure. In combination with a ventricular gallop rhythm, it is accepted as a sign of myocarditis.

Errors sometimes occur in the diagnosis of endocarditis because of incorrect appraisal of the systolic murmur. A systolic murmur with maximum loudness at the apex may also be audible in myocarditis. In such a case it has all the characters of the systolic murmur of relative mitral insufficiency, i.e. it is quiet, of low timbre (blowing), and is heard either at the beginning or only at the end of the systole. It is poorly transmitted to the axillary region.

A systolic murmur most audible over the base of the heart may be purely functional in character even if it is perceived as a musical murmur and resembles the ejection murmur in the character of intensification.

The systolic murmur in endocarditis is characterized by all the properties of the murmur heard in organic mitral insufficiency. It is so loud that it is clearly heard during the entire systole without straining one's hearing. It is usually transmitted well to the axillary region. Sometimes this murmur is heard not immediately after the first sound, but is separated from it by a silent interval. This late systolic murmur is encountered in myocarditis.

A mid-diastolic murmur at the heart apex is a sign of endocarditis only if it is heard at the same time as a prolonged murmur occupying the entire systole. If it appears in a patient with short systolic murmurs (early or late systolic) it is accepted as a purely functional murmur caused by myocarditis.

In some cases of rheumatic carditis a split first sound is perceived on auscultation as a presystolic murmur, while it is at times difficult to distinguish the ventricular gallop rhythm from a mid-diastolic murmur. Phonocardiography may yield very valuable diagnostic information in such cases.

Endocarditis of the aortic valve is manifested by a diastolic murmur first heard in the third and fourth intercostal spaces at the left sternal border. This murmur is at first very weak and inconstant. It may disappear for several days only to appear again. With time it becomes more clearly audible. A diastolic murmur of this localization appears long before the other signs of aortic insufficiency (intensified apex beat, characteristic changes in the pulse and pressure in the peripheral arteries). The appearance of a diastolic murmur at the aortic valve permits a reliable distinction to be made of rheumatic carditis from myocarditis and from neurocirculatory dystonia.

In rheumatic carditis enlargement of the heart occurs gradually within two or three months, and its shape changes. Its waist is often smoothed out and the left atrium is sometimes enlarged. Rapid enlargement of the heart is only encountered in rheumatic pancar-

ditis and is caused by the accumulation of effusion in the pericardial cavity. In neurocirculatory dystonia the heart always retains its normal size and the left ventricle is never enlarged even in a disease of long duration.

A combination of electrocardiographic signs of left-ventricular and left-atrial hypertrophy (gradually developing in rheumatic carditis) suggests that the patient has mitral insufficiency either alone or combined with aortic insufficiency. Unfortunately, these signs are not among those occurring early in endocarditis. They usually appear together with the other clinical and X-ray signs of the heart disease.

The clinical picture of recurrent rheumatic endocarditis is characterized by the same symptoms which are typical of primary involvement of a valve. The diagnosis of recurrent rheumatic endocarditis must be substantiated, just as the diagnosis of primary rheumatic carditis. We cannot agree with those authors who are ready to claim that elevation of body temperature of any duration in a patient with compensated heart disease is necessarily a manifestation of recurrent rheumatic endocarditis and who often ignore other factors, besides rheumatic carditis, to be the cause of decompensation in rheumatic heart disease.

Another extremity is no less misleading, namely, when rheumatic endocarditis is diagnosed only after a heart disease has already formed. Practical experience indicates, unfortunately, that such errors are frequent. In about half the patients rheumatic fever is marked only by affection of the cardiovascular system and its manifestations are so atypical that neither physician nor patient pays attention to them in good time.

The differential diagnosis of rheumatic carditis is also difficult because we still lack a reliable laboratory test like the treponema pallidum immobilization test which would help to distinguish this disease from functionally similar cardiopathy. This is why the diagnosis of rheumatic carditis is still fundamentally a clinical problem. It may only be made after a more or less prolonged follow-up of the order in which the symptoms and their complexes appear.

General weakness, subfebrile body temperature, pain in the region of the heart, and increased ESR may be the only signs of rheumatic carditis for a long time and the physician's task consists in distinguishing them from similar signs encountered in myocarditis, neurocirculatory dystonia, and other diseases.

The true cause of the disease may be identified only after long-term follow-up of the dynamics in the changes of the heart sounds and the systolic murmur, the size of the heart, the character of changes in the configuration of its parts, and the character of the ECG changes. In neurocirculatory dystonia the systolic murmur may be audible for years without changing either in force, in dura-

tion or in timbre. The short systolic murmur in rheumatic carditis gradually intensifies and begins occupying the whole systole. The younger the patient, the more difficult it is to rule out the diagnosis of rheumatic carditis.

Aortalgia

Inflammatory or degenerative lesions of the aorta are often marked by pain which is generally designated aortalgia. Friedberg (1966) and many other authors believe that inflammatory diseases of the aorta, just as its congenital anomalies, are usually asymptomatic and that the complaints of pain or other unpleasant sensations in the chest in these patients should be attributed to complications, the most frequent of which are dilatation of the aorta with the aortic insufficiency syndrome, constriction of the coronary arteries, and aneurysms of the aorta.

Non-specific forms of aortitis are encountered both as an isolated affection and in association with scleroderma, ankylosing spondylitis or lymphogranulomatosis. The chest pain in these diseases is usually mild, of long duration and only in rare cases resembles the pain in angina pectoris.

In arteritis of the aorta and its branches, pain in most cases appears after a long period of subfebrile temperature, moderate leucocytosis, and increased ESR. The disease prevails among young females. Protracted pain in the region of the heart without irradiation is encountered in most cases. The typical angina pectoris syndrome, whether isolated or combined with aortic insufficiency, is very rarely encountered because the inflammatory process is usually localized proximal to the orifices of the coronary arteries and the fibrous ring of the aortic valve. The diagnosis is not very difficult because the chest pain is only one of the signs in the clinical picture of arteritis of the aorta and its branches.

The inflammatory process in syphilis does not spread to Valsalva's sinuses, as a rule, and the chest pain is therefore not always encountered in all cases but occurs approximately only in one fourth of patients with syphilitic aortitis. Syphilitic aortitis sometimes extends to the aortic orifice and to the cusps of the aortic valve, the sclerosis of which leads to aortic insufficiency.

In syphilitic aortitis the coronary arteries are constricted for only a distance of 1 cm (rarely 2 cm) from their orifices. The clinical picture of pain in marked constriction of the coronary artery orifices in a patient with syphilis hardly differs from the clinical picture of angina pectoris in atherosclerosis of the coronary arteries.

In making the differential diagnosis between angina pectoris of syphilitic and that of atherosclerotic origin, the patient's age should be taken into account as well as such characteristic signs of syphilitic

aortitis as distension of the ascending aorta and isolated aortic valve insufficiency. Extracardiac signs of syphilis (positive treponema pallidum immobilization test and syphilitic affection of the central nervous system) are also of considerable differential diagnostic value.

Aneurysms of the aorta, often multiple, are found in 20 to 40 per cent of patients who had died from syphilitic aortitis. The muscle and elastic fibres at sites where the inflammatory process is sharply pronounced are destroyed, the aortic wall here is weak and gradually bulges under the effect of fluctuations even of normal arterial pressure. When aortic dilatation is clearly localized, a sacculated aneurysm forms. A more diffuse dilatation of the aortic wall leads to the development of fusiform aneurysms.

With its growth, the aneurysm exerts mounting pressure on the organs adjacent to the aorta. The character of symptoms arising in this case is determined to a great measure by the localization of the aneurysm, the direction of its growth, and the innervation and function of the adjacent organs. Chest pain in aneurysm of the aorta has two sources: stimulation of receptors embedded in its wall and stimulation of receptors in the organs and tissues adjacent to the aorta.

Slow growth of the aneurysm is attended in about 20 per cent of cases by marked pain or is asymptomatic. Sharp pain in a chest appears only a little before the aneurysm ruptures and sometimes only at the time of its rupture. This pain has no specific features and the association with aneurysm of the aorta may be suspected only because of the attendant symptoms and signs. The character of these concomitant symptoms and signs is mainly determined by the localization of the aneurysm.

Aneurysm of the ascending aorta usually grows to the right and upwards. It sometimes grows to such a size that its pulsation is palpable or even visible in the second or first intercostal space at the sternal border. In some cases it compresses the right bronchus and causes cough and dyspnoea. Erosion of the bronchial or tracheal wall may be attended by mild haemorrhage. In rare cases vena cava superior is compressed and a characteristic network of dilated subcutaneous veins forms on the anterior chest wall. Erosion of the ribs and sternum causes severe pain in the chest.

Aneurysm of the ascending aorta proves to be syphilitic in most cases. Atherosclerotic aneurysms are much rarer than syphilitic in this segment of the aorta. Idiopathic distension of the ascending aorta is very rare. In recent years it has been usually assessed as one of the manifestations of Marfan's syndrome.

Pain in aneurysm of the aortic arch is combined with numerous symptoms consequent upon compression of the trachea (dry cough), oesophagus (dysphagia), left bronchus, left recurrent laryngeal nerve

(hoarse voice), and sympathetic nerves. Moreover, localization of the aneurysm in this part of the aorta often leads to an unequal pulse and signs of inadequate blood supply to the brain with characteristic disorders of vision and tendency to fainting.

Aneurysms of the descending aorta are often asymptomatic. Those growing laterally may become very large without causing any subjective disturbances in health. In medial growth of the aneurysm signs of compression of the roots of the spinal cord and vertebral usure appear. Aneurysms of the arch and descending aorta are of atherosclerotic origin, as a rule.

The clinical manifestations of chest pain of aortic origin may differ noticeably with each patient. The severest pain usually results from pressure of the aneurysm on the adjacent organs. The combination of pain with symptoms and signs of affection of the trachea, bronchi, oesophagus, recurrent laryngeal nerve, roots of the spinal cord, sympathetic nerves or vena cava superior provides the basis for linking it with a lesion of the aorta.

Diseases of Other Chest Organs

Diseases of the Lungs and Pleura

Most people have experienced painful sensations behind the sternum in **acute tracheitis**. The pain is often burning and always intensified during cough. Parasternal pain develops in addition to the retrosternal pain when bronchi are involved in the inflammatory process. Irritation of the trachea at its bifurcation and above this site is attended by pain in the region of the sternoclavicular articulation and anterior surface of the neck.

Study of the characteristic sensations arising during bronchoscopy showed that pain in stimulation of the bronchial mucosa is projected onto the homolateral side of the chest. The afferent fibres from the trachea and bronchi are components of the vagus nerves, evidence of which is the disappearance of pain on the side on which the nerve is divided.

The mucous membrane of the small bronchi and the pulmonary parenchyma evidently contain no pain receptors, because their stimulation and cauterization induce no pain sensations. Tumours originating from pulmonary alveoli may cause no pain sensations even when they grow to a large size. Pancoast's tumour may serve as an example; it causes pain only after growing into the pleura and compressing the sympathetic trunk and brachial plexus.

Tumours arising from large bronchi cause pain, the maximum intensity of which corresponds to the projection of the tumour onto the chest surface. Inflammation of the lung parenchyma is attended by pain only when the parietal pleura is involved in the pathological process.

The afferent fibres from pain receptors lodged in the parietal pleura are part of the intercostal nerves. Their stimulation is perceived as pain in the skin of the chest. It is of stabbing or cutting character and like any skin pain it is clearly localized. Irritation of the parietal pleura covering the diaphragmatic surface of the lungs is attended by pain in the skin of the upper abdomen.

Pleural pain is often encountered in **acute fibrinous pleurisy** which develops in many inflammatory diseases of the lungs. It is a particularly constant occurrence in pleuropneumonia. In focal pneumonia the inflammatory process spreads to the periphery and often reaches the visceral pleura and extends to the parietal pleura. The pain is moderate in most cases and never predominates in the clinical picture of the disease.

Chest pain in **pulmonary infarction** is also explained by reactive inflammation of the parietal pleura, which occurs only when the tissue involved in the infarction extends to the visceral pleura. Pain in **pneumothorax** is often unbearable, but sometimes it may be moderate and like other forms of pleural pain it intensifies in cough and during movements. Spontaneous pneumothorax may sometimes occur without pain.

Bronchogenic carcinoma and other tumours of the lung are sometimes attended by protracted continuous pain in the chest. The origin of this pain is attributed to infiltration of the parietal pleura by the tumorous tissue. The pain in such cases loses connection with the act of respiration. It is experienced with equal intensity day and night, and when the patient holds his breath and when he coughs.

Continuous chest pain is an invariable sign of **primary tumours of the pleura.** Affection of the pleura itself is evidently only one of the causes of this pain. The second cause is infiltration of the sympathetic trunk by the tumour. Stimulation of this trunk explains the intensity of the pain.

The intensity of chest pain in primary inflammation of the pleura varies sharply from one case to another. In some cases it is intolerable, in others, e.g. in some collagenoses, the patient makes no complaints although the pleural rub is clearly audible. Correct appraisal of the complaints concerning pain in the chest and the findings of physical examination make it possible to define the diagnosis of the principal suffering more precisely in such cases.

Diseases of the Mediastinal Organs

The sensations of pain arising in affection of the mediastinal organs are distinguished for their great variety. Acute inflammatory **diseases of the pericardium, perforation of the oesophagus** and **pneumomediastinum** are attended by unbearable pain. The intensity of pain in multiple mediastinal tumours is determined by the extent to which the adjoining nerve structures are involved in the pathological process (sympathetic trunks, posterior nerve roots, the vagus and phrenic nerves).

Many **mediastinal tumours** and **mediastinitis** may be asymptomatic for a long time. The first pain sensations usually appear because of complications, for instance, in necrosis of the tumour or pressure exerted by it on the adjacent organs. A feeling of heaviness, like constriction behind the sternum, appears first which is later joined by cough and dyspnoea. In malignant tumour the sensation of retrosternal constriction is soon replaced by pain which is distinguished by persistence. The intensity of the pain is determined by the extent to which organs adjacent to the tumour are involved in the process. Pressure exerted on the spine often causes pain of the radicular type, whereas involvement of the oesophagus causes pain on swallowing. Fever is very rare; it is attributed to necrosis of the tumour and concomitant mediastinitis which is usually moderate.

Pain on swallowing, particularly of spicy or hot food, is a constant symptom of acute and chronic forms of **oesophagitis**. In peptic oesophageal ulcer pain arises not only when swallowing, but also after eructation. The appearance of pain after a meal is characteristic of a large **oesophageal diverticulum**. The pain itself is felt behind the sternum approximately on a level with the oesophageal lesion and is referred to the back.

Retrosternal pain, very intensive at times, is encountered in **cardiospasm** and **carcinoma of the eosophagus**. It is referred to the neck, upper jaw, and back. It sometimes lasts only a few minutes and closely resembles pain in angina pectoris. At times it is protracted in which event it may be mistaken for pain of myocardial infarction. Identical pain occurs in prolapse of the gastric mucosa into the lower oesophagus. When such pain occurs during a meal and is attended by dysphagia, it is easily distinguished from angina pectoris. When it occurs spontaneously at night unassociated with eating, it is often mistaken for angina pectoris at rest.

A frequently recurring retrosternal pain resembling anginal pain in localization and irradiation may be caused by **spasm of the oesophagus**. The attacks of oesophagospasm in one of our patients often occurred after he had consumed a considerable quantity of alcohol. Predominance of the pain which developed during work and its

fairly rapid disappearance after taking nitroglycerin suggested that the patient had ischaemic heart disease with angina pectoris. The detailed questioning of the patient revealed that the pain was frequently associated with dysphagia. Further observation over the course of the disease and the results of special methods of examination made it possible to establish the diagnosis of oesophageal spasm.

Diseases of the Diaphragm

Chest pain may be of diaphragmatic origin. In rare instances it is attributed to ischaemia of the diaphragm developing because of its protracted and strong contractions. Most often the pain appears with the formation of **diaphragmatic hernia**. Hiatal hernias are among the most common diseases of the gastro-intestinal tract and insufficient knowledge of the painful sensations occurring in these conditions may give rise to diagnostic errors.

Sensory innervation of the diaphragm is accomplished through the phrenic and intercostal nerves. Stimulation of the central part of the superior or inferior surface of the diaphragm is marked by the appearance of pain along the superior border of the trapezius muscle, whereas stimulation of its lateral (anterior, posterior, and lateral) parts gives rise to acute pain in the epigastric or lumbar region or in the right or left hypochondrium.

Chest pain in hiatal hernia is of dual origin. In most instances it develops under the effect of peptic oesophagitis which is often attendant to this disease. The pain is felt in the epigastrium or over the lower third of the sternum and is often accompanied by regurgitation, a sensation of burning, and increased salivation. In other cases chest pain is caused by impaired function of the stomach which often penetrates into the hernial opening. Much less frequently chest pain is a consequence of stimulation of the phrenic nerve by an organ which had penetrated through the hernial opening. This pain is often localized behind the lower third of the sternum and since it is referred to the left shoulder it bears a close resemblance to anginal pain. Exertion with increased intra-abdominal pressure may intensify this pain thus increasing the resemblance with pain in angina pectoris.

Diaphragmatic pleurisy is often concomitant with pneumonia and pericarditis. Acute pain characteristic of pleurisy is felt in such cases in the supraclavicular region or in the hypochondrium on the corresponding side of the body. Like pleural pain of other origin, this pain intensifies during cough and deep breathing. Pain in **subdiaphragmatic abscess** possesses the same features as pain felt in diaphragmatic pleuritis. Depending on the localization of the abscess

it may be felt in the shoulders, hypochondrial regions or in the back.

Diseases of the Chest Wall

Lesions of the Intercostal Nerves

Herpes zoster is the most common cause of acute pain in the intercostal spaces. The disease is caused by a virus. One, rarely two sympathetic ganglia and the peripheral nerves, associated with them, are involved. A sharp burning pain appears first. When an intercostal nerve is affected, the pain spreads over its distribution from the spine to the midline of the body. The pain lasts for a long time, intensifying now and then. Sometimes it precedes the eruption of vesicles by seven to ten days and persists for several months after they disappear. Diagnostic difficulties arise only when herpes zoster occurs on the left side and only in the initial period of the disease before the appearance of the characteristic eruption.

Persistent aching pain in the region of the heart replaced at times by acute stabbing pain appears sometimes after a spinal or thoracic trauma. The pain is caused by stimulation or incarceration of the intercostal nerves by fibrous tissue or the cartilages of the pathologically mobile eighth to tenth ribs. When the patient coughs or turns, these ribs may compress the intercostal nerve and give rise to a sharp stabbing pain.

Dull pain is encountered in most cases with this syndrome which has been aptly called the **slipping costal cartilage syndrome**. Pain in the region of the heart occurs only in luxation of the ribs on the left. A tentative diagnosis is made when hypersensitivity to pressure exerted in the eighth or ninth intercostal spaces on the paravertebral line is revealed. The final diagnosis may only be made from the findings of X-ray examination.

Affection of the Muscles of the Chest and Upper Limbs

Pain in the muscles forming the walls of the chest may be distinguished as local (e.g. pain in haematoma or trauma) or diffuse an example of which is pain in infectious diseases, trichiniasis and fibromyositis. Everybody has probably experienced muscle pain after heavy and long-term exertion. It is particularly common in individuals who are untrained or insufficiently trained. The cause of this pain is still unknown. It may only be presumed that its ap-

pearance is linked with the retention of insufficiently oxidized metabolites. The pain begins four or six hours after inadequately heavy, usually long-term physical exertion and reaches a maximum on the second or third day. Thermal procedures, massage and mild exercise relieve it noticeably.

Persistent dull pain in the muscles of the anterior chest wall sometimes occurs after considerable exertion or for no obvious reason. It is usually felt in the region of the smaller pectoral muscle and the corresponding shoulder joint. It intensifies during exercise. In affection of the left pectoral muscle, the patient attributes this pain to the heart. The connection of the pain with exertion and its noticeable relief by nitroglycerin (Dixon, 1968) create a false impression that it is associated with the condition of coronary circulation.

The complex of symptoms described is generally designated the **anterior chest wall syndrome**. Its causes are not known. It was first encountered in young soldiers who had been subject to considerable physical exertion. We observed it in myocardial infarction convalescents.

The soft tissues of the shoulder girdle are often affected by **fibromyositis** which usually sets in after injury or a chill and, in rare cases, after myocardial infarction. The disease is unilateral as a rule. The bursa subacromialis is involved simultaneously with the soft tissues. The muscle spasm is attended by pain and leads to impaired function and sometimes complete immobilization of the shoulder joint. In some cases, the function of the joint is not restored after the pain ceases, probably because adhesions form between the tendinous capsule of the deltoid muscle and the tissues surrounding it.

Fibromyositis is sometimes localized in the intercostal spaces of both or only one side of the chest. The anterior serratus, the greater and smaller pectoral muscles and the muscle sheaths and fasciae surrounding them are involved in the inflammatory process simultaneously with the intercostal muscles. Sharply tender hard nodules are sometimes palpated in the intercostal spaces in such cases.

The general condition of a patient with fibromyositis is satisfactory, but irritability and easy fatiguability develop because of the continuous pain. The pain intensifies noticeably during movements. Stiffness of the ribs may develop in chronic cases. The muscles are not atrophied in fibromyositis. The pain increases noticeably with weather changes and emotional stress.

The diagnosis of fibromyositis may only be established after all other diseases attended by pain in the muscles are ruled out. One becomes particularly frequently convinced that the underlying factors of persistent muscle pain are arthritis, spondylitis and tumours.

Fibromyositis of the arm must be differentiated from the scalenus anticus syndrome and brachial plexitis.

The **scalenus (anticus) syndrome** results from compression of the upper limb neuromuscular bundle between the anterior and middle scalene muscles, between the anterior scalene muscle and an accessory cervical rib or a normal first rib. The lesion may be unilateral or bilateral. The disease usually begins at middle age acutely or gradually. Females have the disease more often than males.

The clinical picture of the syndrome is diverse. Signs developing due to compression of the subclavian artery and brachial plexus predominate in some cases, neurosis-like conditions with vegetative crises come to the forefront in others. The development of paroxysmal states is explained by stimulation of sympathetic fibres forming the brachial plexus.

The patient mainly complains of pain in the neck, supraclavicular regions, shoulder joints, upper limbs and the anterior chest wall. The lateral surface of the arms and ulnar surface of the forearms are the zones to which the pain is referred. Sometimes the pain appears first in the fingers or hands and then spreads to the proximal parts of the limbs, the supraclavicular and subscapular regions, and the anterior chest wall. The pain occurs in attacks of several minutes to several hours.

The pain may be dull, distending, burning, aching. Sometimes, especially during movements, it is perceived as an electric shock. Exercise intensifies pain, as a rule. The pain is often attended by sensory disorders in the form of numbness, formication, and prickling in the ulnar zone of the hands and forearms. Diminution of muscle strength or increased fatiguability in the distal parts of the limbs, the ring and little fingers in particular, is often found. Hypotonia and hypotrophy of the muscles of the hypothenar and scapular region on the side of the affection are characteristic symptoms. Active movements at the shoulder joint are usually restricted. The tendon and periosteal reflexes on the side of the affection are diminished.

Cardialgia is encountered in bilateral or left scalenus anticus syndrome. The patients usually complain of palpitation paroxysms or of a feeling that the heart has stopped beating. These sensations are sometimes attended by dizziness, dimmed eyes, and at times brief loss of consciousness. Pain in the region of the heart is often accompanied by burning pain in the upper limbs which is sometimes distinguished with difficulty from referred anginal pain. In some instances pain in the hands precedes pain in the region of the heart. This type of pain in left scalenus syndrome is often taken for the peripheral form of angina pectoris.

The vegetovascular disorders have a tendency to spread diffusely in the scalenus syndrome. They are manifested by vegetative crises

during which there are a general chill, troubled respiration, and episodes of general weakness during which the skin turns drastically pale. A feeling of tightness behind the sternum is sometimes experienced. Headache develops at the same time as the crisis and continues for several hours after it has ended. The headache is explained by short-term increase in arterial pressure.

Raynaud's syndrome is a frequent complication of the scalenus syndrome. Paroxysmal coldness and pallor and at times cyanosis of one or both hands may last several minutes to one or two hours. These vegetovascular disorders usually appear after exertion of the shoulder girdle or under the effect of cooling or emotional stress. The skin on the hands and sometimes also on the forearms atrophies and pitting or even oedema of the subcutaneous tissue develops. Necrosis of the distal finger phalanges is very rare, usually found only in patients with thrombosis of the subclavian artery.

In a marked scalenus syndrome the diagnosis presents no difficulty. A less obvious clinical picture of the syndrome must be distinguished from other diseases, primarily from cervical osteochondrosis, arteritis of the aorta and its branches, ischaemic heart disease, tumours of the spinal cord, syringomyelia, and lesions of the ulnar and median nerves.

The pain in cervical osteochondrosis results from stimulation of the fifth to seventh spinal roots, i.e. it spreads along the lateral and not the medial surface of the upper limb. Pain is sometimes elicited by a sharp turn of the head.

Cervical osteochondrosis is attended neither by vasomotor disorders in the upper limb nor by thrombosis of the subclavian artery which is judged by weakening or disappearance of the pulse on the affected side. In the scalenus anticus syndrome there are no changes in the cervical segment of the spine characteristic of osteochondrosis.

Pain in the region of the heart which is referred to the neck and along the medial surface of the left upper limb in left scalenus anticus syndrome is sometimes mistaken for angina pectoris. The true cause of the pain is often identified more easily by thorough clinical analysis of the concomitant symptoms rather than by analysis of the electrocardiographic or other laboratory signs of coronary atherosclerosis. A very diverse set of trophic and vegeto-vascular disorders is often disclosed in the scalenus anticus syndrome but is never encountered in angina pectoris complicating atherosclerosis of the coronary artery. Consultation with a neurologist may help considerably in identifying the causes of the trophic disorders and pain in the limbs in syringomyelia and lesions of the median and ulnar nerves.

Reflex dystrophy of the upper limb (shoulder-hand syndrome) is encountered with approximately the same frequency in myo-

cardial infarction, cervical osteochondrosis, and spondylitis; much less frequently it develops after injury, hemiplegia, herpes zoster, and in patients with bronchial carcinoma. The disease is usually found only in individuals over fifty years of age. Males in the group of patients with myocardial infarction suffer from it more often. In all other groups females are obviously predominant. The syndrome is unilateral in 75 per cent and bilateral in 25 per cent of cases.

In our patients reflex neurovascular dystrophy was consequent upon myocardial infarction, hemiplegia, and carcinoma of the left bronchus. The onset of the disease was gradual in all cases. Other authors report a sudden onset. The arm and hand are usually affected to a different degree. Disorders in the function of the shoulder prevail in some cases and of the hand in others.

Pain in the shoulder, usually moderate, is the earliest symptom. Soon after, the shoulder joint becomes stiff because of the pain and movements are restricted. The limb becomes tender to palpation and slightly enlarged because of oedema of the subcutaneous tissue. Oedema is more pronounced on the back of the hand. The skin here is thin and shiny. Contracture of the fingers and atrophy of the subcutaneous tissue and interosseous muscles develop gradually. Milder cases with spontaneous recovery occur now and then.

In the early stages of the disease the skin on the affected hand is warmer than that on the healthy hand because of hyperaemia. In the later stages hyperaemia disappears and the hand turns cold, pale, and hypersensitive to reduced environmental temperature. The clinical picture of Raynaud's syndrome gradually forms. X-ray usually reveals osteoporosis of the humerus and the bones of the hand, which is always localized in the early stages of the disease, but diffuse in the later stages.

The diagnosis of the ailment usually causes no difficulty only when dystrophy of the shoulder and hand develops in attendance to the diseases indicated above. In all other cases with dystrophy the need arises to consult a neurologist so as to rule out Sudeck's atrophy, neurogenic arthropathy, and some other diseases which have a similar clinical picture.

Diseases of the Bones and Joints

Pain in the chest wall is often caused by pathological processes in the ribs, sternum, and the adjacent cartilages. Sensory nerve endings are found in a particularly large number in the periosteum and its lesions are therefore always marked by intensive and distinctly localized pain. Stimulation of the inner bone surface is only attended by moderate, poorly localized pain.

Diseases of the bone marrow and metastasis of tumours to the marrow are painless until the afferent fibres of the inner bone surface are stimulated. This explains the appearance of dull poorly localized pain in the sternum in myeloma or in late stages of leucoses and the frequent total absence of painful sensations in metastatic spread of malignant tumours to the bone marrow revealed, for instance, by examination of the sternal material obtained by aspiration.

Stimulation of the periosteum in injuries and fractures of bones and in osteomyelitis produces pain of clearly, defined localization. The site of the lesion is easily found on inspection, palpation and in X-ray examination. Pain in subperiosteal haematomas is often short-lived. Pain in osteomyelitis may continue for a very long time.

Chronic inflammatory processes in the bones in tuberculosis, syphilis, and actinomycosis are recognized from the medical history and signs attendant to the pain. Diffuse bone affection in osteomalacia, osteoporosis, and osteogenesis imperfecta is easily demonstrated by X-ray.

Primary tumours of the ribs produce local swelling as a rule, whereas metastatic tumours often cannot be detected either on inspection or palpation. Even X-ray in some cases cannot demonstrate small metastatic lesions of carcinoma or multiple myeloma in the ribs. Fractures of the ribs occurring spontaneously or after an absolutely inadequate trauma may be the first objective signs of this metastasis.

Atherosclerotic and syphilitic aneurysms of the aorta are asymptomatic in most cases and usually revealed during X-ray examination for some other disease. Pain in the bones occurs in approximately 15 per cent of such cases. The pulsed pressure of the aneurysm on the sternum, ribs, and spine is attended by pain of clearly defined localization. Compression of the posterior spinal roots induces pain which is referred to the corresponding dermatome.

An internist very often has to deal with chest pain occurring in association with **osteochondrosis of the cervical spine**. Progressive constriction of the intervertebral disks with the formation of osteophytes and sometimes Schmorl's body may also result in compression of one or more nerve roots.

The disease is usually encountered among the middle-aged and elderly. It begins acutely or insidiously. The patient first experiences brief pain in the neck. The formation of Schmorl's body is attended by sharp pain which is attributed either to some mild injury or an awkward movement of the neck. This pain is characteristically intensified by head movements. It is usually referred along the medial surface of the arm and forearm down to the fingers. Numbness and prickling of the skin and mild atrophy of muscles

of the involved segment often appear simultaneously with the pain.

The gradual onset of the disease occurs more often than a sudden onset. Bedrest intensifies the pain as a rule. This explains the frequent occurrence of pain at night which is sometimes mistaken for nocturnal anginal attacks. The characteristic pain may be induced by pressing the head when it is inclined forward with a half-turn toward the side of the affected limb (Spurling's sign), or by flexing and extending the neck quickly several times (Lermit's sign). The tendon reflexes on the side of the affection are usually slightly diminished.

Compression of the anterior spinal roots weakens the strength of the muscles which they innervate and in severer cases leads to their atrophy. The localization of these disorders is determined by the level of the root compression. Constipation and impaired function of the urinary bladder sphincters develop in the later stages of the disease.

Signs of impaired blood flow along the vertebral artery which passes through the transverse processes of the cervical vertebrae are of considerable diagnostic importance. In sudden turns of the neck, this artery is compressed, sometimes to total obliteration of its lumen. In a healthy person temporary arrest of blood flow through the vertebral artery is compensated by blood flowing through the well-developed collaterals of the circle of Willis. In atherosclerosis of the carotid and vertebral arteries and in compression of the vertebral arteries by osteophytes of the cervical vertebrae insufficient blood is supplied to the brain along the collaterals, as a consequence of which sharp turns of the head often cause dizziness and even brief loss of consciousness.

Osteophytes and narrowing of the intervertebral spaces are normal aging processes and are often encountered in elderly and old persons who have no complaints. Sensory disorders and muscle atrophy in a patient with X-ray signs of osteochondrosis may therefore be caused by some other disease, e.g. tumour of the spinal cord.

Thus, the clinical picture of cervical osteochondrosis comprises the syndromes of posterior and anterior spinal root compression and the vertebral artery insufficiency syndrome. Cervical osteochondrosis with pain predominating in the left shoulder and left upper limb is sometimes mistaken for angina pectoris. Careful questioning of the patient enables this error to be easily avoided. Difficulties arise only when a patient has both cervical osteochondrosis and atherosclerosis of the coronary arteries.

It is far more difficult to differentiate radicular pain in osteochondrosis from radicular pain developing in affection of the spine with tuberculosis, syphilis or metastatic spread of malignant tumours to the vertebrae. Tuberculous and syphilitic affections of the spine are very rare today. Osteomyelitis of the vertebrae consequent upon

furuncles and carbuncles as well as primary vertebral tumours are probably still rarer. Metastatic spread of tumours to the spine from the lungs, kidneys, prostate, thyroid and mammary glands is a much more frequent occurrence. Metastatic tumour of the bones is demonstrated by X-ray in such cases. A primary tumour is very difficult to detect at times, even at the late stages of the disease.

Pain in the neck with radiation to the shoulder and hand is often encountered in tumours of the cervical segment of the spinal cord. A diminution of strength and atrophy of the upper limb muscles and signs of involvement of the pyramidal tracts are usually found at the same time as pain in such cases. The progressive growth of these signs and simultaneous involvement of several roots allow tumour of the cervical spinal cord segment to be distinguished from cervical osteochondrosis.

Sharp radicular pain in the upper limb is sometimes induced by herpes zoster. Fulminant stabbing pain is felt at times in the upper limbs in tabes dorsalis. It is distinguished from pain in cervical osteochondrosis not only by its brevity but because it is unassociated with movements. The presence of locomotor ataxia and other signs of syphilis of the central nervous system makes it easier to identify the true cause of this pain.

In our experience there were patients in whom persistent chest pain of a radicular type was the initial manifestation of tuberculosis of the spine. The destructive changes in the vertebrae were demonstrated on radiographs only several months after the radicular pain had appeared.

Tietze's and the manubrio-sternal syndromes and xiphoidalgia (the xiphodynia syndrome) are among the rare causes of pain in the anterior chest wall. The causes of these syndromes have not been fully explored, probably because of their low incidence.

Tietze's syndrome usually sets in with mild pain which intensifies gradually obliging the patient to seek medical advice. The pain is sometimes preceded by a brief febrile condition which is usually mistaken for acute respiratory infection. The pain appearing after it is sometimes regarded as a 'second disease' and as an allergic reaction to the infection. The greatest pain is felt close to the sternum where it articulates with the cartilages of the second to fourth ribs. The pain intensifies noticeably during exercise and particularly during movements requiring the contraction of the intercostal and thoracic muscles. Even at rest it may be drastically intensified during cough, sneezing, and deep inspiration.

Three or four days after the beginning of pain, a sharply tender hard swelling appears on one or both sides of the sternum. Palpation reveals thickening of the costal cartilages. The cartilages on the left are predominantly affected. The sternoclavicular articulation is sometimes involved. Radiographs in rare cases show foci of osteo-

porosis in the adjacent areas of the rib or sternum. Recovery is spontaneous. The swelling disappears first, and then the pain.

The **manubrio-sternal syndrome** is manifested by attacks of acute pain above the upper part of the sternum or next to it. Swelling of the manubrio-sternal articulation and its tenderness to palpation sometimes occur. The pain intensifies during exercise. In the manubrio-sternal syndrome the pain (like the pain in Tietze's syndrome) increases during cough, sneezing, deep inspiration, and in bending, turning and straightening out of the body.

The manubrio-sternal syndrome is often encountered in rheumatoid arthritis. When pain is the only ailment it is sometimes perceived by the patient and interpreted by the doctor as typical anginal pain.

Pain in the region of the lower third of the sternum and xiphoid process may be regarded as pain felt in the anterior chest wall and the epigastrium in equal measure. Pain of this localization is designated **xiphoidalgia** or the xiphodynia syndrome. It is of a dull character, intensifies with any movement of the trunk, and is sometimes attended by nausea and a feeling of tightness in the throat. The pain increases during exertion and may be referred to the neck, shoulders, and upper limbs; it is sometimes mistaken for anginal pain. Pressure exerted on the xiphoid process may cause both local pain and pain with the indicated radiation.

Affection of the diaphragm, the sternoxiphoid articulation, and the lymph nodes located behind the xiphoid process may be the source of this pain. Xiphoidalgia, like epigastric pain, is encountered particularly frequently in inflammatory diseases of the gall bladder, gastric and duodenal ulcers, perigastritis and periduodenitis.

Other Diseases

The afferent fibres of the **mammary gland** enter the spinal cord as part of the second to sixth intercostal nerves. Some fibres of these nerves are connected with the branchial plexus and the third cervical nerve. Because of these anastomoses pain arising in the mammary gland may spread to the axilla and along the medial surface of the upper limb down to the fingers of the ipsilateral hand. In other cases this pain may spread along the distribution of the intercostal nerves and embrace half the chest, and sometimes it is referred upward to the supraclavicular region and upper half of the neck.

Pain in the mammary gland is commonly caused by inflammation. Acute lancinating pain in mastitis often occurs as short attacks and spreading along the upper limb down to the ring and little fingers resembles anginal pain. Benign and malignant mammary

tumours may follow a latent course for a long time or may cause mild pain.

Pain in fibrous mastopathy ordinarily begins insidiously. At first it is experienced only in the premenstrual period but becomes more intense and continuous later. The referred pain of the indicated localization increases during movements. Many tender thickenings are palpated in the mammary gland. Fibrous mastopathy is characteristically bilateral.

Carcinoma of the mammary gland causes no pain at the beginning. The tumour is always solitary and found in the upper lateral segment as a rule. Lancinating or stabbing pain with typical radiation is experienced in the breast in the later stages of the tumour. It should not be forgotten that the disease is mostly encountered in elderly women in whom the malignant tumour may be combined with ischaemic heart disease.

Mondor's disease, or cord-like thrombophlebitis of the anterior and lateral surface of the chest, appears suddenly in a healthy person or soon after a febrile disease which is usually mistaken for influenza or some other acute respiratory infection (Rusanov, 1975).

The disease prevails among females. Cord-like thickenings 5 to 20 cm long and fused with the skin form on the anterior surface of the chest and the abdominal wall, and sometimes in the axilla. They are moderately tender to palpation and are displaced together with the skin. Body temperature is normal or subfebrile. The tenderness lasts three to seven days. The cord-like structures persist for several months in some cases.

Acute (Intolerable) Chest Pain

Pain is a subjective sensation and the physician judges its intensity mainly from the behaviour of the patients and his ability to analyse his sensations and give a clear oral account of them. Unfortunately, the ability both to analyse one's sensations and to describe them in words depends not only on the cultural level of the patient but also on the intensity and character of the pain. In the internist's practice chest pain is usually a consequence of coronary insufficiency. The degree of its severity in various cases ranges from a simple sensation of discomfort in the precardiac region to an anginal state.

This chapter discusses only those diseases which are usually marked by intolerable pain (Supplement VI, 2). Attempts are often made to distinguish these diseases one from the other only according to the pronounced character of their symptoms and signs accompanying pain. Without denying the value of this methodical procedure, we would like to draw attention to the considerable differ-

ential diagnostic significance of the clinical analysis of the pain itself. Proper appraisal of this subjective sensation, its localization, the degree to which it is pronounced, and the peculiarities of its intensification requires considerable experience on the part of the physician. This is why we hope that the results of our experience described here may prove of value to young physicians who are developing their own approach to the differential diagnosis of internal diseases.

Diseases of the Heart

Myocardial Infarction

In 43 per cent of cases myocardial infarction occurs suddenly. In the remaining cases it is preceded by angina pectoris of more or less considerable duration. According to the results of our analysis, pain is encountered in no less than 70 per cent of patients. In repeated infarction pain occurs almost just as frequently as in the first infarction. Excruciating pain may arise at any time of night or day, but most often in the early hours of the morning.

The pain usually appears when the person is generally feeling well, and soon becomes the predominant factor among the clinical symptoms of the disease. Its appearance is often attended by the fear of approaching death. Males usually try to conceal this apprehension. They often succeed in this at the onset of the disease. In attempting to relieve the pain they toss about in bed or pace the room and try to stifle the growing sensation of constriction in the chest at any cost, but with no success. At the peak of a moderately severe attack the patient usually lies in bed, impatiently changing his position and complaining of pain. This restlessness sometimes continues for several hours and terminates in drastic weakness and loss of vigour.

In infarction, the pain is usually pressing or constricting. In rare cases we encountered rupturing and lancinating pains. At the onset of the disease they are moderately intensive in most cases. After a minute of pain, there is a short period of relief followed by a new attack of pain much more intensive than the preceding one. With each new attack the intensity of the pain grows. In about 30 minutes it reaches maximum and becomes intolerable. The patient can no longer contain himself and starts moaning and crying for help. Sweating and extreme weakness appear by this time.

Mounting and subsiding in waves, the pain persists for hours on end. In more favourable cases, the intervals between the attacks gradually increase with time, while the intensity of pain during

the attack diminishes. The total duration of pain in non-complicated infarction does not usually exceed 24 hours. Sometimes the pain becomes intolerable from the very onset of the disease and even intravenous infusion of such potent anaesthetics as morphine, Fentanyl, or droperidol cannot arrest it effectively. In such cases myocardial infarction is soon complicated by shock.

Maximum pain in myocardial infarction is almost always felt in the precardiac region. In mild cases the pain is usually retrosternal, in severer cases it is diffuse and referred to the shoulder, upper limbs, neck, lower jaw, and even to the interscapular space. We never encountered extensive myocardial infarction with severe extracardiac pain. In our experience, extracardiac pain occurred only in angina pectoris and in localized necroses of the myocardium.

Radiation of pain to the upper abdomen and epigastrium (status gastralgicus) is a relatively rare occurrence. Pain in the upper abdomen is generally attributed to spread of the pain impulses to the neighbouring segments of the spinal cord. We encountered the gastralgic form of myocardial infarction in only 2.7 per cent of cases. In all of them the abdominal pain was attended by pain in the precardiac region. In some cases the precardiac pain was less intense than pain in the right hypochondrium and therefore went unnoticed by inexperienced physicians.

Thus, from the diagnostic standpoint severe pain in myocardial infarction is characterized by a sudden onset for which there seems to be no cause; it increases gradually, and is felt in the precardiac region and is referred upwards to the lower jaw and shoulders, backward to the interscapular space, and downward to the left hypochondrium and upper abdomen.

The pain often predominates in the clinical picture of the initial period of myocardial infarction, other manifestations of the disease are found simultaneously, but as if overshadowed by pain. Signs of the resorption-necrotic syndrome and disorders of heart rhythm are encountered with particular constancy. Other complications (shock, acute heart failure, the abdominal syndrome and cerebrocirculatory disorders) are much less frequent. The steady search for these syndromes may facilitate and assist the identification of the true cause of pain in the chest.

Pain in myocardial infarction is often attended by changes in the heart sounds. A diminished first sound is considered to be a characteristic sign. Its sonorousness at the apex is reduced to that of the second sound; it may even be weaker than the second sound. Both heart sounds are sometimes diminished. In some instances, however, they are clear. An atrial gallop rhythm is audible in the first days of the infarction in about one third of the patients. A ventricular gallop rhythm occurs much less frequently. The third and fourth additional sounds merge sometimes and a quadriple

rhythm develops. The signs listed are inconstant, but their appearance distinguishes the pain in myocardial infarction from pains of extracardiac origin.

Kazembek (1896) drew attention to precardiac pulsation which appears, as it turned out later, in transmural and in non-penetrating infarcts of the left-ventricular anterior and posterior walls. We rarely detected this sign on the first day of the disease, but it was often demonstrated clearly on the second and third days.

The diagnostic significance of the systolic murmur is due to its close connection with the functional condition usually of the left-ventricular papillary muscles. The appearance of this murmur during the attack of pain or soon after it ends suggests subendocardial localization of the infarct.

The pericardial rub arises in patients with transmural infarction on the second or third day after the attack of retrosternal pain. It would be difficult to overestimate its significance, but the true incidence of this sign is still unknown, because it is short-lived in most patients and because conditions for the auscultation of pericarditis localized on the posterior left-ventricular wall are unfavourable.

In most cases of myocardial infarction pain is attended by an increase in the pulse rate to 100-120 per minute. Tachycardia characteristically precedes elevation of body temperature. Bradycardia is often encountered in patients with disorders of conduction.

In cases of mild infarction the arterial pressure is normal and sometimes even increased. Diagnostic significance is attached only to a decrease in arterial pressure, systolic pressure in particular. In a sudden onset of severe infarction arterial pressure reduces noticeably, usually within one to two hours after the pain arises but its lowest values are recorded only on the third or fourth day of the disease.

Disorders of heart rhythm are found in 80 to 90 per cent of cases with myocardial infarction. Some of these arrhythmias are distinguished by their brevity, whereas others having developed in the acute period of the disease become attendant to the patient's condition throughout life. Since disorders of rhythm are regularly encountered in myocardial infarction, the diagnosis is made easier. The development of arrhythmias is not only of diagnostic, but of high prognostic significance. The fatality rate of infarction with marked rhythm disorders is about double that of the disease with a normal heart rhythm (Vinogradov, 1965).

Many disorders of heart rhythm cause no subjective sensations. Even such severe disorder as ventricular tachycardia arises and terminates unnoticeably for some patients. Cardiac fibrillation, impaired atrioventricular conduction, and paroxysmal tachycardia are of particularly high diagnostic value because they are a frequent

occurrence in myocardial infarction and are very rare in pain of other origin.

It is more difficult to appraise the differential diagnostic significance of extrasystole. It is almost always (in 80 per cent of cases) encountered in myocardial infarction, but is also revealed fairly often in acute pancreatitis and in perforating gastric ulcer. The coexistence in one patient of several types of arrhythmias, which are capable of very rapidly replacing one another, is particularly characteristic of myocardial infarction.

Sudden death is such a typical sign of myocardial infarction that it is generally used for making a retrospective diagnosis. If the simultaneous existence of two arrythmias or change of one arrhythmia by another is found in the period when the patient is being observed, myocardial infarction should be regarded as the most probable cause of pain. Ventricular fibrillation or cardiac arrest usually comes to the forefront as the direct cause of sudden death of these patients. Either of these two conditions is almost always preceded by a period (usually brief) of extrasystoles or some other arrhythmia.

If the chest pain is caused by myocardial infarction, some other signs of the resorption-necrotic syndrome may be found in practically each case. Some of them appear in the first hours of the disease, others several days or weeks after its onset. Knowledge of the time when each of these signs developed and the duration of its existence may make it much easier to identify the most frequent cause of severe chest pain.

Acute myocardial ischaemia is now recognized as the principal cause of pain characteristic of myocardial infarction. With the development of necrosis the pain ceases and signs of the resorption-necrotic syndrome begin to gain prominence in the clinical picture.

Ischaemia of the myocardium precedes its necrosis in some cases or exists simultaneously with it in others. In many cases of myocardial infarction chest pain appears before necrosis develops. By the time the patient comes under medical surveillance, signs of the resorption-necrotic syndrome can usually be already revealed because they develop soon after the pain begins as a rule. Every internist encounters cases of myocardial infarction at one time or another in which signs of the resorption-necrotic syndrome are detected only after lengthy periods or in which death occurs before this syndrome develops. Retrospective analysis allows the unusual course of the disease to be linked with disorders of heart rhythm or with the peculiar localization of an infarct that is usually small. An atypical clinical picture is particularly frequent in second infarctions.

The **resorption-necrotic syndrome** is a constant factor of myocardial infarction. The experience gained allows the assertion that the diagnosis of myocardial infarction may only be made in cases in which the other clinical manifestations (pain, abdominal syndrome,

dynamic cerebrocirculatory insufficiency, shock, acute heart failure, arrhythmia) are combined in one way or another at least with some signs of the resorption-necrotic syndrome.

The diagnostic capability of the physician and his skill in making the differential diagnosis at the bedside of a myocardial infarction patient is determined by his ability to divulge and correctly appraise the signs of the resorption-necrotic syndrome, i.e. the complex of signs developing due to resorption of the necrotic focus in the myocardium. In our opinion, the distinction of this syndrome in the clinical picture of infarction is not merely of theoretical interest. It simplifies the understanding of the clinical picture of infarction and makes the diagnosis and differential diagnosis of this disease much easier.

It seems expedient at the contemporary level of our knowledge to distinguish within the framework of the resorption-necrotic syndrome signs of the body's general reaction to the formation of the necrotic focus or foci and the aseptic inflammation in the myocardium and signs of destruction of its contractile tissue and connective-tissue structure.

The **body's general reaction to myocardial necrosis.** Aseptic necrosis of the myocardium is attended by fever, changes in the blood morphological picture, and increased ESR. Body temperature usually rises on the second or third day of the disease. In moderately severe cases it reaches 38°C and stays at this level for three or four days. Fever of long duration always proves to be a consequence of complications of the infarction, usually pneumonia or pulmonary infarction. A febrile reaction is encountered at the onset of the disease in about one third of the patients. It is often absent in old patients and in patients suffering from shock.

The febrile reaction is one of the important diagnostic signs of infarction. It should be borne in mind, however, that this reaction acquires definite diagnostic significance only in context with the clinical manifestations of the disease. Neither the presence nor absence of this reaction in itself provides grounds for establishing or ruling out the diagnosis of myocardial infarction. In other words, diagnostic significance must be attached both to the fever and still more to the background against which it develops.

A few days after the infarction occurs, body temperature returns to normal. The persistence of subfebrile temperature indicates that complications (thromboendocarditis, postinfarction syndrome) have developed.

Aseptic inflammation of the myocardium in its infarct is attended not only by a febrile reaction, but also by leucocytosis. The leucocyte count is increased in most cases, but remains normal throughout the disease in only 10 to 11 per cent of patients. In some cases leucocytosis appears in the first hours of the disease. It is believed

that the level of leucocytosis is determined by the extent of the infarct and is therefore of prognostic importance.

In some cases the leucocyte count returns to normal in a few days, in others—in several months. Long-term leucocytosis or its undulating increase and decrease, like fever of long duration, is encountered when complications develop. The blood leucocyte count increases mainly at the expense of the neutrophils.

The ESR may be normal in the first days of the infarction; it begins to increase in most cases a day or two after the appearance of fever or leucocytosis and remains so till the infarct heals completely.

Disorders of myocardial contractility. Pain of cardiac origin may be quite confidently differentiated from pain of non-cardiac origin by appraising heart function. In 1937 Tennant and Wiggers found that the ischaemic areas of the heart lose their contractility. During systole they either remain immobile or perform paradoxical movements, i.e. they bulge instead of contracting.

Petrosyan and Zingerman (1977) examined a group of patients suffering from myocardial infarction by means of ventriculography. They also noted that the ventricular wall in the region of the infarct did not contract or contracted very weakly. As a result, the left ventricle is incompletely evacuated during the systole. Its diastolic volume grows, while the systolic ejection decreases.

These disturbances in haemodynamics occur in every case induced by severe ischaemia or ischaemic necrosis of the myocardium. They are not found in pain of extracardiac origin.

Zones of myocardial paradoxical movements, akinesia or hypokinesia may also be disclosed by echocardiography which is conducted in clinics for internal diseases because it is safe and sufficiently informative. Echocardiography makes it possible to determine the localization of the infarct in most cases as well as its extent, the contractile function of the whole heart, and the amplitude of movements of the affected and intact myocardial areas.

Paradoxical movements of the heart wall usually occur in the zone of a transmural infarct. They are sometimes encountered as a temporary phenomenon in the first days of an extensive non-transmural infarct. In less extensive infarct, the affected area is akinetic or hypokinetic. On the side contralateral to the affection, the amplitude of myocardial movements during systole and diastole increases noticeably. For instance, akinesia of the anterior left-ventricular wall or hypokinesia of the posterior wall is combined with hyperkinesia of the interventricular septum.

According to Lobanov, a member of our staff, akinesia and hypokinesia occur in the first hours following the appearance of pain. Sometimes they are detected at the same time as *S-T* elevation on the ECG, before abnormalities develop in the *QRS* complex. This

is explained by the fact that the myocardium loses its contractile properties as early as the stage of ischaemia, before the necrotic changes develop in it. Localization of the infarction, according to the findings of echocardiography and of electrocardiography, always coincides. Echocardiography is more advantageous because it also enables the physician to detect affection of the contractile heart function from the volume of the systolic ejection and the amount of residual blood in the heart.

On summing up the data discussed above it can be stated that intolerable chest pain induced by coronary insufficiency, which precedes myocardial infarction, is brief as a rule. In each case of excruciating intolerable pain in the chest either recent extensive infarct complicated by pericarditis or dissecting aneurysm of the aorta should be suspected. If this rule is observed, the diagnostic difficulties in primary infarction will not be difficult to surmount.

The diagnostic difficulties noticeably grow with second infarction because the ECG abnormalities and disorders of heart contractility disclosed on examination of the patient are quite frequently interpreted as the consequence of infarction suffered earlier.

It is our experience that protracted intolerable chest pain is in most cases induced by myocarditis, pericarditis, or extracardiac diseases. Coronary insufficiency may be attended by intolerable pain which, however, is short-lived.

In each case with long-term excruciating pain, direct signs of the resorption-necrotic syndrome of myocardial infarction must be searched for; if such signs are not detected, we regard this pain non-coronarogenic. Many clinicians find this point of view to be extremely orthodox, but the results of the clinical and anatomical comparison which we made provide grounds to consider it sufficiently reliable from the standpoint of practical diagnostics.

ECG changes. The formation of a focus of necrosis or necrobiosis is always attended by a distortion of the normal course of myocardial depolarization and repolarization processes. These changes are best demonstrated on the electrocardiogram and vectorcardiogram. Electrocardiography is more advantageous because it allows simultaneous analysis of automaticity and conduction disorders. The presence of disorders of these functions makes the diagnosis of myocardial infarction much easier. Extensive clinical experience in ECG interpretation in most cases enables not only to disclose foci of fresh necrosis in the myocardium, but to judge their size and localization.

Infarcts of the interventricular septum, and left-ventricular anterior, diaphragmatic, and lateral walls are generally distinguished. Each of these localizations of the infarct is marked by characteristic ECG changes in strictly definite leads shown in Table 1. Infarctions are often encountered in which lesions are found simultaneously

in more than one part of the heart, e.g. anterior and lateral walls, anterior wall and interventricular septum, posterior and lateral walls of the left ventricle. Table 1 shows the leads in which ECG abnormalities are demonstrated making it possible to diagnose infarction of these localizations.

Table 1

Localization of Myocardial Infarction according to the Results of Electrocardiography

Type of infarction (according to localization)	Leads in which abnormalities are found										
	standard			unipolar		chest					
	I	II	III	aVL	aVF	1	2	3	4	5	6
Anterior	±			+			+	+	+		
Anterolateral	+			+					+	+	+
Anteroseptal	+			+		+	+	+	+		
Diaphragmatic		+	+		+						
Posterolateral		+	+		+					±	+
Lateral	+			+							
Septal (anterior part)						+	+	+			
Septal (the whole septum)		+	+		+	+	+	±			

The results of clinical and anatomical comparison provide grounds to presume that necrosis may occur in the myocardium with or without pain in the chest. In most cases precardiac pain precedes the formation of myocardial necrosis, sometimes by a few hours, at other times by 24 hours. In rare cases pain is experienced two or three days before the infarction. In such instances it appears and disappears from time to time and is almost never intolerable.

Irrespective of the duration and intensity of the chest pain, its association with infarction evidently cannot be ruled out on the basis of the results of a single electrocardiographic examination, because one can never be sure that the characteristic ECG changes absent at the given moment will not be recorded a few hours later. In some cases the diagnosis of infarction cannot be excluded even by the results of a series of ECG. Such situations are particularly common in a second infarction, bundle branch block, severe disorders of heart rhythm and in localization of necrosis in the subendocardial coat or in the lateral wall of the left ventricle.

Despite the limitations indicated, the ECG findings make it much easier to differentiate chest pains. The results of ECG are often of decisive importance when infarction has to be disclosed or ruled out. Interpretation of these findings sometimes requires much skill.

In most cases of infarction a necrotic area, a zone of injury and a zone of ischaemia may be revealed. A necrotic area is demonstrated on the ECG by the beginning of negative deflection of the *QS*, *Qr*, *qR* or *QR* type. Wave *Q* reaches 0.04 s in width. Wave *R* is often reduced in size and may even disappear completely.

The zone of injury is determined by the characteristic arched elevation of the *S-T* segment in leads in which there is a deep *Q* wave. *S-T* segment displacement in itself cannot be accepted as an indication of myocardial infarction. It is often found in patients given cardiac glycosides, in those with severe and long-term arterial hypertension (overstrain of the ventricle), in bundle branch block, and in tachycardia. The clear-cut displacement of the *S-T* segment usually in combination with a high *T* wave is sometimes recorded in healthy individuals with signs of marked vagotonia. An elevated *S-T* segment in these patients often returns to normal level after exercise.

T wave reflects the repolarization process, i.e. an entirely different process from that underlying the *QRS* complex. Changes in the *T* wave may therefore be encountered when the *QRS* complex is normal. The zone of ischaemia is displayed on the ECG by a negative or deformed *T* wave. Change in the *T* wave is encountered in many other diseases and cannot be regarded in itself as a direct sign of myocardial infarction.

The electrocardiographic signs of necrosis, injury and ischaemia are only detected in extensive myocardial infarction. The appearance of the *QS* complex is indicative of transmural infarction. An ECG with deep *Q* waves are recorded only when the left-ventricular wall is necrotized for approximately one half or two thirds of its thickness beginning from the endocardium. The *Q* wave is not recorded if the necrosis occurs subendocardially in the left ventricle and extends through less than half of its thickness. In such cases the results of electrocardiography in themselves are of small diagnostic significance.

Extensive primary infarction follows a typical course in most cases and is attended by characteristic ECG changes. Its diagnosis in most cases is not difficult. Unfortunately, this is not true of second myocardial infarction because its clinical manifestations are often atypical and the ECG changes are insufficiently characteristic. The ECG signs of the recent infarction are superimposed in such cases on the earlier existing signs of cicatricial changes in the myocardium. The resulting ECG sometimes proves to be normal, but at other times shows changes as in diffuse myocardial diseases.

The ECG signs of a recent infarction are detected with difficulty when the necrosis occurs on the lateral left-ventricular wall near to the atrium and in patients with right or left bundle branch block. Extensive pericarditis may change the ECG to such an extent that

signs characteristic of the concomitant myocardial infarction are detected on it with difficulty. Atypical ECG changes are often encountered in extensive infarction of the interventricular septum. In such cases the connection of the pain with myocardial infarction may be confirmed only by the results of a series of electrocardiograms recorded in the patient.

Considerable diagnostic difficulties sometimes arise in restricted myocardial infarction often attended by atypical ECG changes. Other methods of examination are resorted to in such cases to identify the cause of the pain. Restricted myocardial infarction is usually attended by moderate pain. This is why it has to be differentiated more often from recent unstable angina pectoris than from diseases marked by intolerable chest pain.

In the early stages of infarction of the anterior left-ventricular wall, a clear-cut *Q* wave and elevated *S-T* segment are recorded on the ECG in leads I and aVL. At the same time, depression of the *S-T* segment in leads III and aVF is found. A coronary *T* wave begins forming later. The *Q* wave is sometimes recorded in lead II.

ECG changes are usually more marked in chest (V_2-V_5) than in standard leads. Sometimes they are demonstrated in the chest leads earlier than in the standard leads. Elevation of the *S-T* segment by more than 2 mm is recognized as a characteristic sign. In later stages of the infarction the *S-T* segment becomes convex and is gradually depressed to the isoelectric line. With the gradual depression of the *S-T* segment, *T* wave at first becomes biphasic and then negative. A deep negative *T* wave often persists for several months and even for years in some cases. The *QRS* complex takes the *qRs*, *Qrs* or *QS* shape. These changes appear at the beginning of the infarction or after the *S-T* segment returns to the isoelectric line.

Deformity of the *QRS* complex is considered a reliable sign of a focal myocardial lesion. In appraising ECG recorded when the patient experiences pain in the chest, it is advisable to bear in mind that this focus may be either fresh necrosis or an old scar; and that a fresh infarction of the anterior wall in patients with left-ventricular hypertrophy is sometimes not attended by deformity of the *QRS* complex, while in patients with right-ventricular hypertrophy a recent infarction may be demonstrated by the *rS* in V_5.

A convex *S-T* segment elevated above the isoelectric line and continuous with a negative sharp *T* wave may be the only ECG sign of infarction of the anterior left-ventricular wall. Diagnostic importance may be attached to this sign only when a series of ECG demonstrates gradual return of the *S-T* segment to the isoelectric line and simultaneous typical changes in the *T* wave. In all such cases the signs of fresh necrosis in the myocardium were confirmed by the results of other examination methods.

Changes of the *T* wave alone characteristic of myocardial infarction, which are verified by a series of ECG, should be linked either with myocardial damage or with the formation of foci of necrosis in the subendocardial coat. These changes may appear in pain of any origin. Their ultimate diagnostic appraisal is made on the strength of the results of all other methods of examination. Characteristic ECG changes in infarction of the diaphragmatic left-ventricular wall are recorded in leads III, aVF and usually in lead II. Some of the ECG components undergo evolution which does not differ in principle from their evolution in infarction of the anterior left-ventricular wall. The simultaneous existence of deep Q_3 and T_3 waves in itself does not yet justify the diagnosis of myocardial infarction, because this also happens in marked left-ventricular hypertrophy and in a transverse position of the heart in the chest.

The probability of infarction of the diaphragmatic surface of the left ventricle increases noticeably if deep *Q* waves are simultaneously recorded in leads III and aVF, especially in cases in which a negative *T* wave is recorded simultaneously with *Q* wave in aVF, the width of which is at least 0.04 s and its depth is at least 40 per cent of the height of *R* wave.

ECG changes in chest leads in infarction of the diaphragmatic left-ventricular wall usually possess small diagnostic significance because they record action currents which are perpendicular to the vector plane. In the early stages of the infarction a temporary and usually moderate change in the *S-T* segment can nevertheless be noted, while the *T* wave becomes sharp and high. Spread of the infarction to the lateral left-ventricular wall is demonstrated by deep *Q* waves, decreased voltage of *R* waves and characteristic changes in the *ST-T* complex in V_5 and V_6.

The ECG method of examination often cannot disclose an infarct in an area of the posterior left-ventricular wall between the diaphragm and left atrium because the deflection vector occurring in this case is not recorded in the standard lead; it is recorded well in the chest leads, particularly in V_1 and V_2.

The appearance of a high *R* wave in V_1, usually followed by a high *T* wave, is considered typical. The *R/S* ratio in V_{1-2} proves to be more than unity. Some authors pointed out that exactly the same changes in *R* wave are seen in right-ventricular hypertrophy. The diagnostic importance of T_1 wave is also doubtful in many cases because in a healthy person it may be both positive and negative.

High infarct of the posterior left-ventricular wall may be marked by severe pain. The ECG changes are often insufficiently convincing and neither verify nor rule out this localization of the infarct with any confidence. The final diagnosis of the disease in such cases must be mainly based on the results of other methods of examination.

The characteristic ECG changes in infarction localized mainly

or exclusively in the lateral left-ventricular wall are recorded in leads aVL and I. Mild changes are sometimes demonstrated in lead II. When the infarction is localized on the lateral wall of the left ventricle near to its apex, the ECG demonstrates abnormal *Q* waves in aVL and usually in V_5 and V_6. If the necrosis occurs on the lateral wall of the left ventricle close to the atrium (high lateral infarction) a deep and broad *Q* wave is usually recorded in lead aVL and often in lead I.

Change in *Q* wave in lateral infarction is usually pronounced more clearly than the change in the *ST-T* complex and is of great diagnostic importance. *ST* elevation or depression is mainly associated with subendocardial or subepicardial localization of the necrosis.

Lateral infarction may be attended by severe pain. The ECG changes in many cases of this infarction are very moderate and often insufficiently convincing for making the final diagnosis. The findings of other methods of examination may be of great assistance in the diagnosis of lateral infarction and consequently in identifying one of the causes of the severe chest pain.

Infarction of the anterior part of the interventricular septum often extends to part of the adjacent anterior left-ventricular wall and the characteristic changes in the *ST-T* complex may be recorded in chest leads I to IV. *QR*-type deformity of the *QRS* complex is usually demonstrated in chest lead I or II, or only in V_2 or V_3, or even V_4. The *Q* wave is considered pathological if its depth exceeds one quarter of the *R* height in the same lead. The *QRS* complex in these leads often acquires the *QR* shape with the normal height of wave *R* maintained in V_1.

The characteristic ECG changes in infarction of the whole interventricular septum (from the anterior to the posterior heart surfaces) consist of the signs of anteroseptal infarction noted above (see Table 1) in combination with diaphragmatic left-ventricular infarction.

In intraventricular septal infarction the chest pain may be very severe. In identifying its cause one must take into account that massive infarction of this localization is often attended by bundle branch or atrioventricular block. Although the ECG signs of the infarction are usually insufficiently convincing, the sudden occurrence of arrhythmia and marked disorders of conduction nevertheless make it easier to identify the true cause of the pain.

It is far more difficult to rule out myocardial infarction as the cause of pain in patients with chronic right or left bundle branch block. The development of necrosis in most such cases is not attended by new changes in the *QRS* complex, and the only ECG signs of the infarct often prove to be as follows: characteristic evolution of the *ST-T* complex during the disease, *T* wave inversion, and the appearance of *Q* waves in the right chest leads in right bundle branch block or in left chest leads in left bundle branch block.

The results of electrocardiography in such cases acquire diagnostic significance only in association with the data of the medical history and the findings of other methods for identifying myocardial infarction. The results of electrocardiography, scintigraphy and tests for the activity of creatine phosphokinase and its cardiac fraction become particularly valuable.

Second myocardial infarction may be attended both by moderate and by intolerable chest pain. In identifying the cause of the pain, the same difficulties as those in primary myocardial infarction are encountered. The difference consists in a different appraisal in principle of the results of electrocardiography. In every case it is essential to distinguish ECG changes occurring under the effect of fresh necrosis from those caused by foci of scar tissue remaining after a previous myocardial infarction.

The combination of new focal myocardial lesions with old lesions causes great polymorphism of the ECG, which obviously hinders the records being grouped in a system. Shishkin (1933) distinguished three types of ECG changes in second infarction: (1) under the effect of fresh necrosis new changes appear on the ECG in addition to the signs of the old foci either at the same site or in a new heart area; (2) in some cases ECG changes caused by the new necrosis fully conceal the signs of the previous myocardial infarction; (3) fresh myocardial infarct sometimes leads to total disappearance of the ECG signs of the old infarct. If we should add that in many cases there is no characteristic evolution of the ECG signs in the course of the disease, it becomes clear why the possibilities of the electrocardiographic method of examination in the diagnosis of a second myocardial infarction are limited.

On summing up the abovestated it may be concluded that severe pain in the chest, in the precardiac region in particular, is mostly associated with myocardial infarction. The clinical methods of examination permit only a tentative diagnosis of the disease to be made. The final diagnosis must be based on the detection of the direct signs of necrosis of the heart muscle the entirety of which we designated the 'resorption-necrotic syndrome'. The electrocardiographic and some biochemical and systemic signs of this syndrome are of particularly great importance in the diagnosis of myocardial infarction.

Electrocardiography makes it possible in many cases to confirm the association of severe pain with myocardial infarction. There are still quite a few cases, unfortunately, in which the results of electrocardiography neither reject the possibility of myocardial infarction nor allow it to be excluded from the causes of severe pain sensations in the chest.

Particularly many diagnostic errors are made because of the widespread false conception to the effect that the classical ECG signs

of infarction must be recorded in each case of this disease marked by severe chest pain. In studying this problem Coodley (1969) could not find a deep *Q* wave in almost 50 per cent of patients with verified myocardial infarction. The results of purposeful search for other signs of the resorption-necrotic syndrome are often of essential aid in the final solution of this difficult diagnostic problem.

Enzymatic diagnosis of infarction. The muscle cells of the heart are rich in enzymes some of which (e.g. lactate dehydrogenase, aldolase) are found in the cytoplasm, while others (e.g. deoxyribonuclease) are present in the nuclei. Some of the enzymes (e.g. aspartate aminotransferase, AsAT) are located both in the cytoplasm and mitochondria. A certain amount of intracellular enzymes is always contained in the blood serum of a healthy person. They enter it from the destroyed formed elements of the blood and endothelial cells. In addition, enzymes (e.g. creatine phosphokinase) may enter the extracellular space during muscular exertion as a consequence of increased permeability of the cell membranes.

After entering the blood serum, enzymes with a low relative molecular mass (e.g. amylase) are excreted by the kidneys. Enzymes possessing a high molecular mass are either inactivated in the serum or destroyed by the cells of the reticuloendothelial system. Some enzymes noticeably differ from others by the rate of their disappearance from the blood. Creatine phosphokinase activity, for instance, reduces by half within the first six hours, whereas lactic dehydrogenase (LD) activity remains practically the same during the first 24 hours.

Thus, intracellular enzymes enter the blood serum as a consequence of cell destruction and because of reversible disorders of permeability of the cell membranes. The content of enzymes in the blood serum is determined by the ratio of the rates of their entry and inactivation.

The cells of all organs contain almost the same enzymes but their concentration in individual organs is different. The myocardium contains a large amount of AsAT and a small amount of alanine aminotransferase (AlAT), whereas in the liver these enzymes are contained in approximately equal amounts. In the skeletal muscles there is a large amount of creatine phosphokinase and a lesser amount of Al-AsAT; the liver is rich in AlAT, but contains a negligible amount of creatine phosphokinase.

Clinical experience accumulated to date permits the assumption that the determination of enzyme activity in blood serum significantly helps in the diagnosis of myocardial infarction, particularly those forms in which there are no characteristic ECG changes. Much experience has been accumulated by now in the clinical interpretation of the results of tests for the activity of AsAT and AlAT, LD, hydroxybutyrate dehydrogenase and creatine phosphokinase. The

final judgement on the diagnostic significance of other enzymes may be passed after accumulating more extensive data on the results of their application in the clinic.

AsAT has long been used in the diagnosis of myocardial infarction. Its activity in blood serum begins rising in the first hours after infarction and reaches maximum on the second day. In about three or four days after the onset of the disease its activity returns to normal level. AsAT activity is increased in 66 to 96.5 per cent of cases with clinically verified myocardial infarction. False positive results of this test are encountered in approximately 9.5 per cent of cases. Their causes are numerous and cannot always be taken stock of easily. AsAT is present not only in the heart muscle, it is found in large amounts in the skeletal muscles, liver, pancreas, kidneys and brain. Acute lesions of these organs, just as diseases of the heart, may be attended by increased blood transferase activity.

AsAT activity may increase in acute diseases of the abdominal organs; hepatitis, cholecystitis, pancreatitis, and infarcts of the small or large intestine the clinical picture of which may resemble that of acute infarction. AsAT activity noticeably increases in acute mononucleosis, shock and sometimes after treatment with morphine, anticoagulants, penicillin, oxacillin and in the postoperative period.

AsAT activity is sometimes found to be normal in patients with myocardial infarction when the test is made during status anginosus. The blood in such cases was probably taken for the test before necrosis had developed. Daily tests for enzyme activity undoubtedly increase the number of coincidences of positive results of this test with the clinical diagnosis of myocardial infarction.

LD is widespread in all organs and tissues. Its activity in blood serum begins increasing in about six to eight hours, reaches maximum at the end of the third day of the infarction, and remains increased for one or two weeks. LD (like AsAT) is among the nonspecific indications of infarction because its activity is elevated in myocarditis, acute benign pericarditis, diseases of the liver and biliary tract, pulmonary embolism, myositis, haemolytic anaemias, and some infectious diseases.

LD is found in blood serum in five molecular forms which may be isolated from each other by the thermal, chemical or immunological method. The myocardium mainly contains the first LD isoenzyme. Large amounts of this isoenzyme are also found in the red blood cells. That is why even minimum haemolysis in a sample of collected blood leads to false positive test. The relatively late increase in the activity of LD and its isoenzymes in the blood serum is a major shortcoming of the test. Test for activity of the cardiac LD isoenzyme may be recommended not for the early diagnosis of myocardial infarction but for verifying the diagnosis of this dis-

ease on the third or fourth day after the pain occurs. Bluzhas et al. (1976) checked the diagnostic value of total LD activity and the activity of its cardiac fraction on a large number of patients. The tests were performed on the first, second, third and seventh days of the disease. The activity of LD and its cardiac fraction was found to be increased in all cases of transmural infarction but remained normal in 5.2 per cent of cases with non-transmural infarction. The results of the tests were false positive in 6.8 per cent of patients.

Hydroxybutyrate dehydrogenase (HOBD) is mainly found in the heart muscle. Its activity in infarction changes just as frequently as the activity of the LD cardiac fraction. The main advantage of HOBD consists not as much in its high specificity as in the fact that its activity stays increased much longer than the activity of AsAT and LD. The HOBD/LD ratio is of great differential diagnostic importance; it is always above normal level in myocardial infarction but below normal level in hepatitis.

HOBD activity reaches maximum on the third or fourth day of the disease. In myocardial infarction this test yields positive results more frequently than the tests for AsAT and LD. This is probably best explained by the fact that in myocardial infarction HOBD activity stays increased longer than AsAT and LD activity by one or two weeks. False positive tests are encountered in 5.2 per cent of cases. The test for HOBD activity may be recommended for retrospective checking whether or not the correct diagnosis had been made and not for early diagnosis of infarction.

Creatine phosphokinase (CPK) is found in all muscle cells. In the skeletal muscles it is present as a muscle isoenzyme (MM dimers) and in the myocardium as a cardiac fraction (MV dimers). CPK activity in blood of a healthy person is mainly due to its isoenzyme contained in the skeletal muscles. Myocardial infarction is marked by an increase in both total CPK activity and in the activity of the cardiac fraction of this enzyme.

Total CPK activity begins growing four to six hours after the beginning of the disease and in six to eight hours exceeds the initial level four- to eightfold. Maximum CPK activity is found 15 to 26 hours after the onset of the disease. The activity of the cardiac fraction changes in like manner. According to Zhuravlyova, a member of our staff, its activity in the blood of a healthy person ranges between traces to 4-5 per cent of total CPK activity. In extensive myocardial infarction the cardiac fraction may account for as much as 17.2 per cent of total CPK activity. The activity of the cardiac fraction begins rising 4-5 hours after the pain occurs and reaches maximum 3-6 hours ealier than total CPK activity. This is explained by the earlier liberation of the cardiac form of the isoenzyme from the myocyte cytoplasm.

The absolute values of total CPK activity and the activity of

its cardiac fraction are determined by the extent of the myocardial infarction. Total CPK activity in cases with a large myocardial infarct stays increased for four to six days, in a restricted infarct for three to four days. The activity of the cardiac fraction returns to normal level earlier than total CPK activity by one or two days. This is evidently explained by the more rapid removal of the cardiac fraction from the blood.

The increase of total CPK activity alone is always encountered after mild injuries to the skeletal muscles (e.g. after intramuscular injections of drugs), ventricular defibrillation, in haematoma formation, and even in muscle tremor attendant to delirium tremens. CPK in the form of the MV isoenzyme is mainly contained in the myocardium, though a small amount is also detected in the skeletal muscles. The release of the MV fraction into the blood explains the cases of false positive increase in the activity of the CPK cardiac fraction in crushing of the muscles, extensive and deep burns and dermatomyositis. These diseases differ sharply from myocardial infarction in the clinical picture, and in suspected myocardial infarction the test for CPK activity acquires, therefore, high diagnostic significance. To increase the diagnostic value of the test, it is recommended to determine not only the total activity of CPK, but also activity of its cardiac isoenzyme. Simultaneous increase in the activity of the cardiac fraction allows one to speak with assurance of injury inflicted precisely to the myocardial cells. It is our experience that the diagnostic value of a series of tests conducted simultaneously for the activity of CPK and its cardiac fraction is by no means inferior to that of a series of electrocardiographic records.

Other methods of diagnosis. In the last few decades new methods for the diagnosis of myocardial infarction have been suggested. A series of echocardiographic studies, scintigraphy of the myocardium and tests for the concentration of protein-carbohydrate complexes in blood are the most promising. Repeated echocardiography reveals the characteristic dynamics of changes in the contractions of the damaged and intact areas of the infarcted myocardium and makes it possible to forecast in the first days of the disease the possible formation of a ventricular aneurysm. Calcium ions are released in the necrotic myocardium. On binding with intravenously infused ^{99m}Tc pyrophosphate they form in the zone of necrosis clearly demarcated foci of radioactivity which, according to Chazov et al. (1977), may be demonstrated on the scintigrams on the first day of the disease. These authors used this method also for retrospective diagnosis and for determining the size and localization of the myocardial infarct.

In our clinic Sychova and Rylova confirmed these data and showed that the test may yield false negative results. Such results ar

explained by the arrest of the blood flow in the region of the infarct. In such cases ^{99m}Tc pyrophosphate had no access to the zone of the necrosis because of total obturation of the afferent artery and poor development of collaterals. The uptake of ^{99m}Tc pyrophosphate by the myocardium is usually detected in the first six to ten days of the disease. In aneurysm and large scars in the myocardium it is revealed for a lengthy period of time.

When the pain syndrome terminates in the formation of an infarct the necrotic material ultimately begins to resolve and an inflammatory reaction develops in the prenecrotic zone. The regular course of this inflammatory reaction was studied in detail by Smolyannikov and Naddachina (1963) and others.

The inflammatory reaction in the prenecrotic zone of the myocardium is first manifested by the release of segmented leucocytes which are later joined by macrophages and lymphoid and plasma cells. This is followed by the formation of young granulation tissue in the inflammatory zone; with time this tissue develops into mature connective tissue.

It was established that the consecutive change of the morphological picture of the inflammatory reaction is attended by regular changes in the metabolism of some connective-tissue components, certain mucoproteins, and glycoproteins in particular. Changes in the metabolism of chloride-soluble mucoprotein are especially indicative. The content of these protein-carbohydrate complexes in the blood of myocardial infarction patients grows noticeably on the second day of the disease and reaches maximum between the third and seventh days. It stays on a high level for two or three weeks and then begins diminishing, returning to normal level on the sixth to eighth week of the disease.

In macrofocal myocardial infarction the concentration of chloride-soluble mucoprotein in the blood exceeds the initial level about threefold. The long duration of this increase makes the determination of chloride-soluble mucoprotein a very valuable diagnostic test. This test, unfortunately, is also not sufficiently reliable. The blood chloride-soluble mucoprotein content increases not only in myocardial infarction, but in pneumonia as well. Other diseases which often attend myocardial infarction have no effect on the content of protein-carbohydrate complexes.

The tests for enzyme activity and content of protein-carbohydrate complexes in the blood are non-specific diagnostic tests. Their negative results do not rule out the diagnosis of myocardial infarction, while their positive results do not always verify this diagnosis because they may be influenced by extracardiac factors. False positive results are induced particularly often by a concomitant disease of the liver. Acute heart failure in myocardial infarction may lead to the development of central lobular necroses of the liver.

This results in increased activity of AsAT, LD and many other enzymes contained in the hepatic cells. The content of chloride-soluble mucoprotein in the blood in such cases stays normal. The activity of enzymes contained mainly in the muscle cells always increases after surgical interventions, but the content of the intracardiac CPK fraction remains normal.

Simultaneous tests for chloride-soluble mucoprotein and activity of some enzymes, better still isoenzymes contained in the myocardium, make it possible to avoid false positive responses of these tests and thus to come nearer to a more exact identification of the cause of the pain syndrome.

A simplified conception of the interrelationship of the pain syndrome and myocardial necrosis underlies the second source of the erroneous diagnostic conclusions. Coronarogenic pain in the chest, even very intensive, may precede myocardial infarction by several days and even weeks. The opposite is also encountered, when the infarction occurs before the subjective sensation of pain in the chest. In some cases myocardial infarction occurs in two stages and not one. For instance, subendocardial anteroseptal infarction develops first and then grows to a transmural anterolateral infarction in two or three days. The results of clinical methods of examination do not always permit establishing the exact date of the origin of the necrosis. Normal activity, e.g. of CPK and its intracardiac fraction, may be encountered both when the infarction has not yet developed and in an infarct of three to five days duration. Simultaneous tests for the concentration of chloride-soluble mucoproteins and the activity of other enzymes (e.g. hydroxybutyrate dehydrogenase) may actually improve the accuracy of myocardial infarction diagnosis.

In the practice of an internist of an urban polyclinical hospital myocardial infarction proves to be the cause of severe chest pain in about half of the patients making this complaint. This explains the special attention focussed at some of the details of the pain syndrome in myocardial infarction. When severe chest pain develops, myocardial infarction is the first thing that comes to mind, but its diagnosis may only be made when fresh disorders of myocardial contractility are demonstrated on the echocardiogram or signs of the resorption-necrotic syndrome are found simultaneously with the pain. In each case either electrocardiographic and biochemical or electrocardiographic and scintigraphic signs of the infarct must be simultaneously disclosed. Unless these signs are detected the diagnosis of infarction is now considered to be insufficiently substantiated.

Pericarditis

Unbearable pain in the region of the heart or behind the sternum is sometimes encountered in acute pericarditis. Approximately three fourths of all cases of this disease are caused by Coxsackie, influenza, chickenpox, parotitis, measles or infectious mononucleosis viruses or are manifestations of tuberculosis or rheumatic fever. In the remaining cases acute pericarditis is one of the syndromes of systemic lupus erythematosus, myocardial infarction, injury, uraemia or malignant tumour. In rare cases acute pericarditis develops under the effect of radiotherapy or pyogenic and other infections.

The clinical manifestations of pericarditis result from inflammation of the pericardium which at first is almost always fibrinous, and from accumulation of fluid and compression of the heart. Pain, pericardial friction rub and characteristic changes of the electrocardiogram and echocardiogram are the principal signs of the disease.

Pain in the upper chest is combined with epigastric pain. It is often referred along the phrenic nerve to the left arm and left supraclavicular region. The chest pain is attended by fever and pericardial friction rub. The true cause of the pain syndrome is identified more easily if some of the features of its combination with the fever and the results of instrumental examination have been registered.

Pain in the chest in pericarditis may be of the same localization as pain in some forms of myocardial infarction. It is rarely intense, but no diagnostic significance should be attached to this sign because pain in myocardial infarction is not necessarily severe but may hardly be perceptible. The association of pain with movements is important diagnostically. Pain in myocardial infarction does not depend on the patient's position in bed, whereas pain in pericarditis intensifies during movement, turning of the body and change of position in bed. It is often noticeably relieved when the patient changes from a recumbent to a sitting position.

Pain in myocardial infarction usually precedes fever and increased ESR, whereas in acute pericarditis pain appears simultaneously with these signs. In most cases of pericarditis weakness, elevated body temperature, toxicosis and other signs of an influenza-like disease appear a few days prior to the pain syndrome.

The pericardial friction rub in myocardial infarction may be brief and soft, whereas in pericarditis it is always clearly audible, usually for one or two weeks. A similar rub is encountered in the postinfarction syndrome.

It is sometimes hard to distinguish ECG changes in infarction from those in acute pericarditis. In studying the ECG, special attention should be focused at the following signs.

1. The *S-T* segment is elevated in all standard and chest leads in the first days of pain suffered by a patient with pericarditis. A few days or weeks after the onset of the disease the *S-T* segment is depressed to the isoelectric line, while the *T* wave becomes negative. Thus, in pericarditis the *T* wave is negative not in the acute period of the disease, but only after the *S-T* segment returns to the isoelectric line. In myocardial infarction the *T* wave becomes negative long before the *S-T* segment is depressed to the isoelectric line.

2. Deep and broad Q_1 and Q_3 waves in combination with characteristic changes in the *ST-T* complex are a typical sign of anterior or posterior myocardial infarction. In pericarditis the *Q* wave is either not recorded or is slightly outlined in the standard leads.

3. In the initial period of pericarditis, the *S-T* segment is concave and, which is particularly typical, elevated in all three leads. In myocardial infarction the *S-T* segment deflects in opposite directions in leads I and III.

4. In pericarditis the *R* wave is almost always recorded in the chest leads, only its amplitude is reduced. In myocardial infarction the *QRS* complex may be so distorted that the *R* waves may disappear.

5. *S-T* elevation in standard leads is sometimes encountered in myocardial infarction complicated by pericarditis. In such cases, however, deep Q_1 or Q_3 waves and typical negative T_1 or T_3 waves are recorded.

In later stages the diagnosis of pericarditis may be made from the results of roentgenokymography. Heart contractions are usually not recorded in pericarditis. A series of radiographs show changes in the size and shape of the heart. The recently suggested method of radioisotope scanning of the heart and liver with human serum albumin and colloid gold also facilitates the detection of effusion in the pericardial cavity.

The echocardiographic method for disclosing the effusion is particularly valuable and simple. With the accumulation of fluid in the pericardial cavity the echo from the anterior chest wall is clearly separated from the echo from the anterior right-ventricular wall. With the accumulation of fluid behind the heart a considerable distance forms between the echocardiogram tracings corresponding to the posterior left-ventricular and pericardial walls (Feigenbaum, 1973).

The analysis of signs attendant to the pain syndrome often renders considerable assistance in making the differential diagnosis of pericarditis and myocardial infarction. Evidence of simultaneous affection of other organs (e.g. pleurisy with effusion, myalgia, arthritis, encephalomyelitis and enlarged lymph nodes) is detected in most cases of pericarditis induced by viruses.

Assessment of the results of tests for enzyme activity in blood

serum calls for particular caution. AsAT or LD activity is increasep in approximately 14 per cent of cases of pericarditis caused by Coxsackie viruses (Herschman and Hammer, 1974). We have no information at our disposal concerning the content of protein-carbohydrate complexes in the blood of patients with pericarditis.

Serological tests are as yet insufficiently applied and are accessible to far from all hospitals. Nonetheless, in all doubtful cases the hospital can always send the material to the district sanitary and epidemiological station for determining the antibody titre or for isolating the culture of the causative agent from the throat mucus or from the faeces. The diagnosis may be considered convincing if a pure culture is isolated or fourfold increase in type-specific neutralizing or complement fixating antibodies is detected. The results of a single examination are regarded convincing if the antibody titre is 1:32 or higher.

The postinfarction syndrome or pleuropericarditis usually occurs suddenly on the 3rd or 4th week of the disease. In most cases pericarditis begins with acute pain in the chest (in the region of the heart and left side of the chest). Pain may appear in the left shoulder when the diaphragm is involved in the process. The pain is often intolerable, lancinating and is intensified during inspiration and change in the body's position. It is attended by fever and the pericardial and pleural friction rubs which are replaced by signs of effusion into the pericardial and one or both pleural cavities.

Pericarditis is evidently the principal cause of the precardiac pain in Dressler's syndrome. Pain often makes the physician meditate the possibility of second myocardial infarction. The association of pain with respiration and the appearance of pneumonia and pleural friction rub simultaneously with it allow the postinfarction syndrome to be distinguished from second myocardial infarction.

The postinfarction syndrome is usually marked by moderate or high leucocytosis; there are no ECG changes characteristic of pericarditis in most cases, but repeated electrocardiography is required for ruling out a recent infarction. No regular patterns are noted in the changes of transferase activity in the postinfarction syndrome.

When making the differential diagnosis between the postinfarction syndrome and repeated myocardial infarction particular attention should be attached to the features of the pain syndrome described above and to the results of repeated electrocardiography. ECG signs indicating that new foci of necrosis have formed in the myocardium are not found in the postinfarction syndrome.

Repeated echocardiographic examination obviously proves to be always very valuable because it makes it possible to divulge new foci of dyskinesia in the myocardium in some cases of infarction and free fluid in the pericardial cavity in Dressler's syndrome.

Scintigraphy of the myocardium following the prescription of technetium pyrophosphate is a reliable modern method for disclosing a recent infarct. The accumulation of pyrophosphate in the necrotic foci is clearly demonstrated as early as the first to third day after its development.

A second infarction which had occurred after the period mentioned may be diagnosed in most cases from the appearance of fresh foci of radioactivity in the myocardium. The occurrence of a second infarction at earlier periods may be revealed on a series of scintigrams from the change in the intensity and size of the radioactive foci in the myocardium.

The postinfarction syndrome is characterized by persistent fever and pericardial friction rub and by the involvement of the pleura, lungs and synovial membranes in the process. Rapid disappearance of pain, fever and other clinical manifestations of the illness one or two days after the prescription of steroid hormones confirms the diagnosis of the postinfarction syndrome. This diagnosis is finally verified when a recurrence occurs soon after the steroid hormones are discontinued.

Myocarditis and Cardiomyopathy

Acute myopericarditis induced, for instance, by Coxsackie viruses may develop into chronic myocarditis. Its course is characterized by periodical exacerbations during which fever, leucocytosis and precardiac pain are encountered. After myocarditic cardiosclerosis develops, each new exacerbation with typical pain in the heart has to be differentiated from recent myocardial infarction. They are distinguished in that diffuse affection of the myocardium occurs in inflammation and focal in infarction. This difference is best demonstrated on heart scintigrams and on echocardiograms. In myocardial infarction ^{99m}Tc pyrophosphate accumulates in the zone of the necrosis which is clearly demarcated, as a rule. The results of echocardiography indicate that in infarction the zone of dyskinesia is attended by a zone of increased myocardial mobility on the opposite side of the ventricle. These signs, typical of focal heart affection, are usually not encountered in myocarditis.

It is particularly difficult to distinguish myocarditis in which coalesced clearly demarcated foci of fibrous tissue localized usually in the subendocardium occur against the background of diffuse foci of this tissue. Their origin is connected with thromboses of the small intramural arteries or Thebesius' veins of the heart. It is easier to make the differential diagnosis in such cases if the functional condition of the adjacent myocardial areas is appraised. Their function is always disturbed in myocarditis but preserved in infarction. Echocardiography discloses this in many instances.

The principal differential diagnostic significance should nonetheless be attached to the differences in the clinical course of these two diseases. Unfortunately, this authentic criterion is not among the early differential diagnostic criteria.

Unbearable chest pain also occurs in congestive and hypertrophic forms of cardiomyopathy. In all cases in our experience this pain was marked by persistence. Having once occurred, it lasted for several hours diminishing and intensifying alternately. Though radiation was atypical in most cases, the appearance of acute left-ventricular or right-ventricular failure after a series of pain attacks suggested atherosclerotic cardiosclerosis with a recent or previously suffered myocardial infarction. The older the patient, the more probable seems this assumption.

In hypertrophic cardiomyopathy the pain syndrome is often attended by paroxysmal dyspnoea and even pulmonary oedema. Electrocardiography often records deep *Q* waves in standard leads II and III and in aVF and V_{1-3}. Signs of delayed intraventricular conduction of the type of bundle branch block or anterior hemiblock are usually simultaneously disclosed.

When combined with the pain syndrome and paroxysmal dyspnoea, these ECG changes are often interpreted as signs of myocardial infarction.

In many cases the final diagnosis can only be made after following the course of the disease. Intensive and often persistent pain in hypertrophic cardiomyopathy does not lead to the development of a full picture of myocardial infarction. No new changes typical of a recent infarction appear on the ECG. The concentration of the CPK or LD cardiac isoenzymes in the blood remains normal. New foci of dyskinesia are not recorded on the echocardiogram and no fresh foci of necrosis are demonstrated on the scintigram.

Besides these methods of examination, the negative results of which allow the diagnosis of myocardial infarction to be ruled out, a complex of methods aimed at verifying the diagnosis of hypertrophic cardiomyopathy must be resorted to.

The pain syndrome is observed in hypotrophic cardiomyopathy attended by a systolic murmur. Signs of disturbed intraventricular conduction and sometimes also shortening of the *PQ* segment with a delta wave are revealed almost in all cases of this disease. The pain syndrome in hypertrophic cardiomyopathy terminates in the development of heart failure, whereas in ischaemic heart disease it terminates in myocardial infarction. Echocardiography and ventriculography are the most reliable methods for the detection of hypertrophic cardiomyopathy. The results of these methods of examination are analysed in detail in the chapter 'Heart Failure'.

Congestive cardiomyopathy in elderly patients is often mistaken for ischaemic heart disease complicated by myocardial infarction.

This error is easily avoided if attention is paid to the size of the heart. Cardiomegaly is actually a constant sign of congestive cardiomyopathy and chronic myocarditis. In myocardial infarction the heart is often of normal size, its enlargement is only found in patients with arterial hypertension, aortic stenosis and left-ventricular aneurysm.

Heart failure in primary myocardial infarction is almost always left-ventricular. In second infarction it is at first also left-ventricular. Failure of the right ventricle develops in attendance to left-ventricular failure usually no earlier than the second or third day of the disease, i.e. always after the development of the infarct. Heart failure in congestive cardiomyopathy and myocarditis is biventricular from the onset, as a rule. In congestive cardiomyopathy the signs of right-ventricular failure often precede the pain syndrome.

It is our experience that tests for enzyme activity in blood serum have no much differential diagnostic significance. Acute heart failure and the concomitant congestion of blood in the liver and pulmonary infarction may cause increased activity of the enzymes in blood serum. Tests for the activity of hydroxybutyrate dehydrogenase and the cardiac fractions of creatine phosphokinase and lactate dehydrogenase may be very helpful. It is important to follow the character of changes in the activity of these enzymes occurring with time. If the first test was made at the onset of the pain attack, repeated tests in a patient with myocardial infarction reveal gradual growth and a similar gradual diminution of their activity in blood. Such a type of dynamics in the activity is encountered neither in myocarditis nor in cardiomyopathy.

ECG changes are observed practically in all cases of cardiomyopathy. The development in the myocardium of more or less extensive areas of fibrous tissue particularly often leads to intraventricular block (left bundle branch block, as a rule), the formation of a pathological Q wave, flattening or inversion of the T wave and displacement of the S-T segment. The results of only a series of ECG may help in making the diagnosis. Myocardial infarction is marked by a typical evolution in the shape and size of the T wave. In cardiomyopathy the ECG changes but slightly with time.

The gallop rhythm is of particular diagnostic significance. There has not been a single case of severe congestive cardiomyopathy in our practice without a gallop rhythm. The absence of the gallop rhythm should be considered as evidence against cardiomyopathy.

The solution of the question concerning the cause of the cardiac pain must sometimes be postponed to a later time. The final diagnosis in such cases is guided by the results gained from studying the features of the clinical course of the disease, i.e. from analysing the signs which appear in attendance to the pain syndrome. It is

necessary in all cases not only rule out the diagnosis of myocardial infarction, but to substantiate the diagnosis of myocarditis or cardiomyopathy. The regular features of their course and the diagnostic methods are discussed additionally in the chapter 'Heart Failure'.

Diseases of the Aorta

Extremely intensive pain in the chest occurs in impaired intactness of the aorta which may be caused by haemorrhage into its wall or its partial or total rupture. Rupture of the inner aortic coat is encountered most commonly; it may be followed by the formation of a false or dissecting aneurysm.

Reports have been made in the last decade on the successful surgical management of these complications. Timely diagnosis is an indispensable guarantee for the prevention of total aortic rupture, threatening every patient with aneurysm of the aorta or incomplete rupture of its wall.

The most commonly encountered immediate causes of aortic rupture are injury, haemorrhage into the muscular coat of the aortic wall, and progressive thinning of the wall because of a gradually growing aneurysm.

Dissecting Aneurysm of the Aorta

Dissecting aneurysm of the ascending aorta. Extremely intensive chest pain is characteristic of dissecting aneurysm of the aorta, quite a rare disease, which is still traditionally considered to be among the complications of coarctation of the aorta and degenerative connective-tissue diseases such as osteogenesis imperfection and Marfan's and the Ehlers-Danlos syndromes.

The data obtained by our staffer Assistant-Professor Zenin pertaining to 156 cases of this disease bear evidence that atherosclerosis is the most common cause of dissecting aneurysm of the aorta.

Long-term arterial hypertension in elderly and old individuals with signs of atherosclerosis leads to degenerative changes in the middle coat of the aorta irrespective of Marfan's syndrome. This evidently explains the association noted by all researchers between the formation of a dissecting aortic aneurysm and persistent, usually high, arterial hypertension, as well as extreme physical exertion.

It is believed that dissecting aneurysm of the aorta begins with a haematoma in the middle coat which forms because of impaired intactness of the small vessels supplying the aortic wall. The internal aortic wall usually ruptures at the site of or close to an atherosclerotic plaque. Blood entering under the intima causes dissection

of the aortic wall. In most cases about one half or three fourths of the aortic circumference is dissected. Dissection of the aortic wall along its entire circumference with the formation of a double-lumen aorta, i.e. an aorta consisting of two tubes, one inserted into the other, is very rare. Zenin found it in only 1.2 per cent of cases.

The formation of a dissecting aortic aneurysm terminates in rupture usually of the outer and sometimes of its inner coat. Signs of internal haemorrhage into the pericardial cavity, lungs, mediastinum and left plural cavity appear in the first case; the formation of a double-lumen aorta occurs in the second. If the initial rupture occurs in the ascending aorta the dissection of its walls may spread both distally, i.e. in the direction of the intravascular blood flow, and proximally, i.e. in the direction of the heart. In rupture of the descending thoracic aorta, its wall is dissected only in the distal direction.

The clinical picture of dissecting aneurysm of the aorta is extremely diverse. It comprises the signs caused by rupture of the aortic wall and signs consequent upon this rupture.

The rupture of the aortic wall in itself is attended by excruciating pain the origin of which is attributed to stretching of the pain receptors lying mainly in its adventitium. The intramural haematoma causes dilatation of the ascending aorta. Distension of the fibrous ring of the aortic valve and the development of aortic insufficiency are encountered in some cases. Body temperature is subfebrile in most cases and only in rare instances it rises to 38-39° C.

Dissection of the wall may be attended by obstruction of arteries arising from the aorta (innominate, common carotid, subclavian, intercostal arteries and the coronary arteries of the heart). The pain syndrome in such cases is accompanied by signs of insufficient supply of blood to organs receiving it through these arteries.

Moderate anaemia appears at the onset of the disease and grows with the enlargement of the haematoma. The formation of a dissecting aneurysm of the aorta, like other acute haemorrhages, is attended by tachycardia, leucocytosis and signs of centralization of the blood flow (skin pallor, oliguria). Since dissecting aneurysm of the aorta is a rare disease, physicians at first attempt to associate the sudden intolerable pain with more common diseases of the heart or lungs. Dissecting aortic aneurysm is usually mistaken for myocardial infarction. The diagnosis of myocardial infarction was made in 52 of 55 cases with dissecting aneurysm of the ascending aorta. Such a large number of errors is explained not only by the similarity of these diseases in their clinical picture, but also by the fact that both diseases mainly affect the same contingent of patients.

Dissecting aneurysm is mostly encountered in the ascending aorta. If it is borne in mind that the ascending aorta is partly localized in the pericardial cavity and shares innervation with the heart it

becomes clear why in practice dissecting aneurysm of the aorta has to be most frequently differentiated from myocardial infarction with a marked pain syndrome. The differential diagnosis of this disease is very difficult particularly when the aneurysm ruptures into the pericardial cavity. The diagnostic problem in such cases is mainly explained by the rapid course of the disease. In the rarely encountered cases of subacute dissecting aneurysm of the aorta, the physician has time for a fuller and sometimes repeated examination of the patient.

The detection of the following features of the clinical picture of these two diseases contributes to establishing a correct diagnosis in such cases.

In dissecting aneurysm of the aorta the pain always occurs suddenly. Its intensity is at a peak at the beginning of the disease, i.e. at the moment when the inner aortic coat ruptures. Periods of the intensification and diminution of pain are noted later. These may be linked with the wave-like process of dissection of the aortic wall. In myocardial infarction pain may also be sudden, but it is usually less intense in the initial period of the disease. As it is noted above, gradual intensification of pain is typical of myocardial infarction.

In most cases with dissecting aneurysm of the ascending aorta pain is first felt behind the sternum and in the region of the heart, and in more than half of the patients it is referred to the back, shoulder blades and interscapular space. Migration of pain along the vertebral column down to the lumbar and sacral regions is particularly characteristic. We encountered a patient in our practice in whom retrosternal pain was first referred only to the back, a few hours later to the lumbar region, and still later to the loins and medial surfaces of the thighs. This peculiar irradiation of pain is explained by spread of the haematoma along the aorta adjoining the vertebral column.

Thus, pain at the onset of dissecting aneurysm may be similar to that in myocardial infarction in localization. It is distinguished from pain in infarction by the character of its intensification and radiation to the back. Radiation of pain along the spine is a very frequent occurrence in dissecting aneurysm of the aorta but is not encountered in myocardial infarction.

Wave-like intensification and abatement of pain is a characteristic sign of dissecting aneurysm of the aorta. In many cases the intensified chest pain may be referred to new regions. For instance, at first the precardiac pain is referred only to the neck and back. During a consecutive period of intensification it is felt not only between the shouder blades, but in the lumbar region and even in the scrotum.

In dissecting aneurysm of the aorta, the sharp pain syndrome does not lead to the development of acute left-ventricular failure,

as a rule. Such failure is a characteristic complication of myocardial infarction marked by a similar or even less severe pain. Hurried shallow breathing is quite often encountered in dissecting aneurysm, but in not a single case of this disease was pulmonary oedema or severe attack of cardiac asthma (frequently attendant to myocardial infarction) observed.

The results of physical and special methods of examination are of invaluable assistance in making the differential diagnosis between infarction-like form of dissecting aortic aneurysm and myocardial infarction. Special importance should be attached to the results of repeated measurement of the vascular bundle breadth. Rapid distension of the vascular bundle is a pathognomonic sign of dissecting aneurysm, but is never encountered in myocardial infarction.

Dilatation of the ascending aorta is detected most easily by X-ray. A double-contour shadow of the aorta is a pathognomonic sign of aneurysm dissection. This sign, unfortunately, is very rarely detected. Zenin found it in only two out of 55 patients suffering from the infarction-like form of dissecting aortic aneurysm. In recent years this cardinal sign of the disease is revealed on the echocardiograms in some cases.

The diagnostic criteria of dissecting aneurysm recorded on the echocardiogram comprise dilatation of the root of the aorta, thickening of the walls of the aorta, and a double shadow of the anterior or posterior aortic wall. Only the last of these signs should be considered characteristic, the first two being often revealed in individuals with no signs of an aortic lesion. It should be borne in mind that dilatation of the ascending aorta may also be disclosed during a physical examination of the patient. Rapid distension of the vascular bundle may be determined by percussion, whereas dilatation of the aorta in the region of its arch is palpated as a pulsating tumour in the jugular fossa.

The results of auscultation are also of high differential diagnostic significance. A systolic murmur appears over the base of the heart in approximately a fourth of the patients suffering from the infarct-like form of dissecting aortic aneurysm. It is distinguished from the systolic murmur often audible over the base of the heart in atherosclerosis of the aorta by the fact that it is clearly heard on the back along the spine.

In about 15 per cent of cases with dissecting aneurysms of the ascending aorta, the systolic murmur was attended by a diastolic murmur that had not been heard previously. The appearance of this murmur is explained by the development of acute aortic insufficiency as the result of distension of the fibrous ring of the aortic valve. In dissecting aneurysm of the ascending aorta, aortic insufficiency is usually mild and does not lead to the appearance of such vascular signs of this syndrome as an abrupt and running pulse,

continuous arterial sound, Quincke's capillary pulse or Duroziez's double murmur.

The ECG is normal in about one third of cases with the infarction-like form of dissecting aortic aneurysm. In the remaining cases the ECG records signs of coronary insufficiency or signs of focal changes in the myocardium. Persistence of these signs on successive ECGs is characteristic of dissecting aortic aneurysm. Dynamic ECG changes typical of myocardial infarction are not demonstrated. Progressive anaemia is a constant occurrence in dissecting aneurysm of the aorta, but is not typical of myocardial infarction.

On summing up the abovestated, the conclusion may be drawn that the pain syndrome predominates in the clinical picture of dissecting aneurysm of the ascending aorta and that, like in myocardial infarction, it is always combined with leucocytosis. The main features distinguishing this disease from myocardial infarction are that the pain and leucocytosis occurring both when the aneurysm forms and in the later stages are not combined with the ECG changes typical of myocardial infarction.

Great diagnostic significance should also be attached to the arterial pressure level and cardiac rhythm. Persistence of severe pain and leucocytosis in myocardial infarction is complicated by hypotonia and the development of cardiogenic shock, as a rule. Protracted pain in dissecting aneurysm of the ascending aorta usually does not lead to the development of hypotonia. Arterial pressure in such patients is almost always high. Various types of arrhythmia occur often in myocardial infarction and very rarely in dissecting aneurysm of the ascending aorta.

Dissecting aneurysm of the descending aorta is an extremely rare disease. We failed to find any works devoted specially to the differential diagnosis of dissecting aortic aneurysm of this localization in the available literature. In our clinic Zenin analysed the clinical picture of 26 cases with dissecting aneurysm of the descending aorta which in 25 patients proved to be a complication of generalized atherosclerosis with predominant affection of the aorta, and in one patient it was a complication of syphilitic aortitis. In all cases the disease began with severe intolerable chest pain lasting from two to nine days and terminating in collapse caused by bleeding from the aorta. The blood escapes into the left pleural cavity or the tissue of the left lung. This localization of the bleeding is explained by the position of the aorta in the posterior mediastinum.

The descending aorta stretches along the left border of the spine which counters the accumulation of blood on this side of the aortic wall, thus preventing its dissection and, therefore, its rupture. The part of the aortic circumference facing the left lung undergoes dissection.

Blood accumulated in the left pleural cavity in every other pa-

tient. Simultaneous bleeding into the left lung and into the pleural cavity was encountered less frequently. Haemorrhages into the posterior mediastinum and right pleural cavity were far more rare.

In accordance with the three principal localizations of the bleeding, rupture of the descending aorta was attended by the syndrome of blood accumulation in the pleural cavity, pulmonary haemorrhage, and the syndrome of haemorrhage into the posterior mediastinum with compression of the organs located in it.

Dissecting aneurysm of the descending thoracic aorta sets in with intolerable pain in the entire chest or just in its left half. Simultaneous retrosternal pain is noted in rare cases. The pain is referred to the back and left hypochondrium. A few hours after its onset, maximum pain moves to the interscapular space and left hypochondrium. Radiation of pain, often down to the lumbar region, is also characteristic. Severe pain is sometimes felt in the right hypochondrium in later stages of the disease. It is caused by rupture of the dissecting aneurysm into the right pleural cavity.

Dyspnoea and anaemia in dissecting aneurysm of the descending thoracic aorta are so vividly manifest, that strike the physician's attention during the first examination of the patient. Hurried and shallow breathing and the unusual pallor of the skin and visible mucous membranes at the onset of the disease could be attributed to the severe pain syndrome, but the pain may be temporarily relieved, whereas dyspnoea and pallor of the skin and mucous membranes do not disappear at this time, but, on the contrary, continue to mount. Internal haemorrhage underlies their steady progress.

At the onset of the disease blood is deposited in the aortic wall. Later, the loss of blood into the pulmonary tissue, mediastinum and pleural cavities begins. In aneurysm of the descending aorta, the thoracic aorta is usually dissected over a considerable distance and anaemia is therefore easily detected at the beginning of the disease. Signs of haemolytic anaemia sometimes appear as the result of the destruction of red cells in the aneurysmal cavity. The severity of anaemia in the later stages of the disease is determined by the amount of the blood loss in rupture of the external aortic coat.

Dyspnoea in dissecting aneurysm of the aorta is evidently not just merely a consequence of blood loss. Mechanical and reflex factors play a major role in its genesis. These are compression of the bronchus by the growing aneurysm, compression atelectasis of the lung developing after haemothorax, and rapid displacement of the mediastinum. As the result of the joint action of these factors, dyspnoea becomes the second most manifest sign of dissecting aneurysm of the descending thoracic aorta in approximately 70 per cent of cases. Dyspnoea is attended by dry, usually persistent, cough when the growing aneurysm compresses the sites of tracheal and bronchial division.

Haemoptysis and haemothorax are reliable but, unfortunately, late diagnostic signs of dissecting aneurysm of the aorta. They appear only after rupture of the aneurysm into the pulmonary tissue or into the pleural cavity. External rupture of the aneurysm into the posterior mediastinum is accompanied by as if inexplicable extravasations into the subcutaneous tissue of the left half of the chest and into the base of the neck. Hypotonia occurs at the moment of aortic rupture, making the examination of the patient extremely difficult or impossible. Frequent diagnostic errors are made as a consequence of this.

The correct diagnosis was suspected in only two of 26 cases with dissecting aneurysm of the descending aorta and even in these two cases the dissecting aneurysm was diagnosed as the second of two possible diseases. In all the other cases it was mistaken for a mediastinal tumour, tumour or tuberculosis of the lungs, acute lobar pneumonia, and embolism of the pulmonary artery. X-ray examination of the aorta would doubtlessly have made it easier to identify the true cause of the affliction in all cases, but in the first hours of the disease this examination is postponed till the patient's condition improves, whereas after external rupture of the aorta it usually cannot be carried out because the patient's condition is extremely grave.

X-ray examination of a patient with dissecting aneurysm of the descending thoracic aorta shows considerable widening of the median shadow and unusual bulging of the descending aorta into the left lung. In two of our patients the aortic shadow had a double contour. Small aneurysms of the descending aorta are best seen in the left oblique position, because in the anteroposterior position they are hidden by the heart shadow. Large aneurysms are easily demonstrated in the anteroposterior position. Contrast X-ray examination is resorted to in cases presenting a diagnostic problem. The size of the aneurysm, its extent, and, sometimes, a double-contour aortic wall are seen on the aortograms.

Most errors in the diagnosis of dissecting aneurysm of the aorta are mainly explained by delayed X-ray examination. The number of such errors may be made noticeably less if we make it a rule to suspect dissecting aneurysm of the aorta in every elderly patient admitted to the clinic because of sudden excruciating pain in the chest with the above-indicated radiation and migration. In sharp chest pain not only repeated (every two or three hours) ECG recording and tests for enzyme activity should become routine forms of examination, but repeated appraisal of changes in the pulmonary respiratory sounds and boundaries of the heart dullness and repeated tests for haemoglobin concentration.

Dissecting aneurysm of the descending thoracic aorta is most frequently mistaken for some chronic disease of the lungs or mediastinum. A diagnosis of bronchial carcinoma or mediastinal tumour

complicated by haemorrhagic pleurisy was usually made in elderly and old patients. The diagnosis of pulmonary tuberculosis was made in patients in whom the protracted course of the disease was previously attended by repeated pulmonary haemorrhage. Haemoptysis in such cases is mistaken for a new haemorrhage. Haemothorax either remains unrecognized, or is mistaken for haemorrhagic pleurisy.

Dissecting aneurysm of the aorta is distinguished from these diseases by an acute onset. The pain syndrome in it occurs not only suddenly but is characterized from the onset of the disease by a degree of intensity never encountered in bronchial tumour or pulmonary tuberculosis. In carcinoma of the bronchus or tumours of the mediastinum, haemorrhagic pleurisy develops in far advanced stages of the disease, when signs of the tumour and its metastasis to other organs are evident. Moreover, haemorrhagic pleurisy usually sets in insidiously. Signs of compression of the mediastinal organs develop acutely in dissecting aneurysm of the aorta. Pain is attended by difficult swallowing because the oesophagus is compressed, continuous cough and a hoarse voice. In tumours of the mediastinum, these signs usually develop gradually and not abruptly. The patient becomes used to these disorders and often does not even draw the physician's attention to them.

In dissecting aneurysm of the aorta, haemothorax appears suddenly in the process of observation over the patient and not before admission to the clinic as is characteristic of pulmonary tuberculosis. Dissecting aortic aneurysm begins abruptly, takes an acute course and terminates unfavourably within a matter of days or weeks. Tuberculosis and tumours of the lungs and mediastinum follow a course more chronic in character.

Acute lobar pneumonia, like dissecting aneurysm of the descending thoracic aorta, sets in abruptly, but analysis of the pronounced character of the symptoms during the disease allows the two afflictions to be distinguished. Acute lobar pneumonia begins with a chill and fever in most cases and the pain syndrome is less severe than that in dissecting aneurysm of the aorta. Repeated physical examination discloses characteristic dynamics of its auscultatory and percussion signs. X-ray examination distinguishes these two diseases.

Embolism of the pulmonary artery begins suddenly and may be complicated by dyspnoea, haemoptysis and collapse which may resemble the picture of collapse complicating rupture of dissecting aortic aneurysm. Pulmonary arterial embolism differs from dissecting aneurysm of the aorta in the character of pains. Pain in embolism of the pulmonary artery is less intensive, does not have a wave-like character, and shows no tendency to migrate along the spine. An important differential diagnostic sign is cyanosis, which is typical

of embolism of the pulmonary artery; in dissecting aneurysm of the aorta, it is not cyanosis that is characteristic, but pallor of the skin and mucous membranes. The results of electrocardiography and X-ray may help considerably in the differential diagnosis of these diseases. Dilatation of the descending aorta is disclosed from the very onset in one of them, signs of acute overexertion of the right ventricle and often signs of infarction of the lungs are detected in the other.

On summing up it may be concluded that the main signs of dissecting aneurysm of the descending thoracic aorta, which distinguish it from other diseases of the chest, are as follows: sudden appearance of intolerable pain in the chest with the peculiar course mentioned above, consistently growing anaemia and dyspnoea, and dilatation of the descending thoracic aorta. The typical complications are haemorrhages into the mediastinum, pleural cavities, and the lung tissue.

Rupture of Aneurysm of the Thoracic Aorta

Intolerable pains usually precede rupture of chronic aneurysm of the aorta which may be congenital or acquired. Congenital aneurysm is most frequently localized in the aortic sinuses, in the ascending aorta, and immediately below the left subclavian artery. Aneurysm of the aorta is a particularly common occurrence in Shereshevsky-Turner's, Ehlers-Danlos and Marfan's syndromes and in stenosis of the aortic isthmus.

Marfan's syndrome is a congenital disease. Its principal signs are an abnormally tall stature, disproportionately long limbs, congenital ectopy of the lens of the eyes, kyphosis, dolichocephalism, keeled chest, long 'spider' fingers, laxity of the joints and, in most cases, an inguinal hernia. Excretion of mucopolysaccharides in the urine is increased.

Connective-tissue deficiency in Marfan's syndrome is most pronounced in the aorta. Its middle coat is always rich in mucoid substance, the structure of which is drastically abnormal. The elastic framework of the aortic wall suffers most. Ruptures of the elastic fibres, mucoid degeneration of the basic connective-tissue substance, and microcystic degeneration and necroses of the middle coat are often found. Weakening of the aortic wall as a result of these changes leads to the formation of aortic aneurysms, usually in the ascending segment or in Valsalva's sinus. Rupture of the intima is usually accompanied by the formation of dissecting aneurysm of the aorta.

The Ehlers-Danlos syndrome is manifested by cardiomegaly, laxity of the joints, and remarkably elastic skin in which even the smallest injuries cause numerous petechiae and ecchymoses. Connec-

tive-tissue disintegration in this syndrome leads to weakening of the arterial wall, as a consequence of which aneurysms of Valsalva's sinus and dissecting aneurysms of the aorta form.

Congenital aneurysms of the descending aorta are usually found in the region of its isthmus. They are particularly common in Shereshevsky-Turner's syndrome. Though coarctation of the aorta is a congenital disease, the aneurysms complicating it develop only after birth.

In rupture of congenital aortic aneurysms the pain syndrome is less severe than that in rupture of a dissecting aneurysm in a patient with atherosclerosis of the aorta. This is explained by the gradual thinning of the aortic wall attended by degeneration of all nerve endings embedded in it.

Acquired aneurysms are encountered far more often than congenital aneurysms. Most of the acquired aneurysms are atherosclerotic in origin. Though infectious aneurysms may form in any part of the aorta, syphilitic aneurysms nonetheless predominate in the ascending aorta, while mycotic aneurysms are mostly found in Valsalva's sinus, patent ductus arteriosus and areas of the aorta on which reconstructive operations had been carried out.

In rupture of a chronic acquired aneurysm the pain syndrome is manifested very vividly. A sacculated aneurysm is particularly apt to rupture. With the growth of these aneurysms, their wall gradually thins out. Rupture was preceded by intensification of pain in all our cases. From long-term observation of the patients it may be noted that progressively growing aneurysm of the aorta is marked by wave-like intensification of pains. Brief periods of excruciating pains are replaced by more or less long periods during which only moderate pain is experienced. In threatening rupture of the aneurysm, the pain becomes unbearable and almost continuous.

The localization of the aneurysm has decisive influence on the clinical picture developing after its rupture.

The wall of a congenital aneurysm of the Valsalva's sinus is so thin that its rupture causes no sharp pain sensations in some cases. Rupture of a mycotic aneurysm of Valsalva's sinus is preceded by excruciating pain which, when intensified, cannot be relieved even by morphine.

In threatening rupture pain is sooner caused by penetration of the aneurysm into the thickness of the myocardium. The pain in rupture of the aneurysm is evidently caused by injury to the aorta, epicardium, myocardium and endocardium. Immediately after the rupture the pain subsides, marked dyspnoea and aortic insufficiency appear; the severity of the signs of this insufficiency is determined by the amount of blood returning from the aorta to the heart cavity.

The patient's condition noticeably improves after the catastrophe.

Dyspnoea disappears or becomes less pronounced. The further course of the disease is determined by the amount of blood returning through the aorta-cardiac shunt.

Aneurysms of Valsalva's sinus take a latent course and the characteristic picture of their rupture in congenital aneurysm develops as if in sound health whereas in syphilitic aortitis or protracted septic endocarditis such an aneurysm is first interpreted as a sudden complication of these diseases, e.g. mycotic embolism of the coronary artery. The pain syndrome has no specific signs and hardly differs from that in dissecting aneurysm of the ascending aorta. The true cause of the precardiac pain becomes evident only after acute aortic insufficiency develops.

Normal creatine phosphokinase activity and a normal ECG differentiate rupture of an aneurysm of the Valsalva's sinus from myocardial infarction. Normal breadth of the aortic shadow distinguishes rupture of Valsalva's sinus aneurysm from dissecting aneurysm of the ascending aorta. These two diseases also differ in their clinical course.

Aneurysms of the ascending aorta, sacculated in particular, are usually of syphilitic origin. Most aneurysms of the descending aorta are of atherosclerotic aetiology. Their wall is extremely thin but ruptures very rarely. A few months prior to rupture severe pains are suffered, the localization and radiation of which are determined by the site of the chronic aneurysm. Rupture of the aorta is usually easily recognized in such cases.

Aneurysm of the Thoracic Aorta with Compression of the Adjacent Organs

Most acquired and congenital aneurysms of the thoracic aorta cause no marked disorders in the patient's subjective well-being. Latent (painless) development is particularly typical of aneurysm of the descending aorta. Approximately half the cases with diffuse or sacculated aneurysms of the ascending aorta are marked by mild pain behind the sternum or in the back. Aneurysm of the arch of the aorta often manifests itself for the first time by signs of compression of organs in the posterior mediastinum.

Severe chest pain is rare in aneurysm of the aorta. It is usually felt in sacculated aneurysms which cause erosion of the sternum, clavicle and ribs or compress the roots of the spinal nerves. Intolerable pain in diffuse aneurysm of the ascending aorta of syphilitic origin is induced both by the lesion of the aortic wall and by the concomitant stenosis of the orifices of the coronary vessels.

The diagnosis of diffuse aortic aneurysm may be suspected on the basis of only a single clinical examination. Dilatation of the

vascular bundle which protrudes particularly to the left in the second or first intercostal space is a characteristic sign. Distension of the aortic ring leads to the appearance of a diastolic murmur related to aortic insufficiency. A systolic murmur is always audible at the same time as a diastolic murmur.

The auscultation findings in aortic insufficiency developing in attendance to diffuse dilatation of the ascending aorta differ from those in insufficiency of the aortic valve of other origin in the character of the second heart sound and the peculiar conduction of a diastolic murmur.

In dilatation of the ascending aorta, the second heart sound is intensified and has a metallic hue, whereas in valvular insufficiency it is usually diminished. In aortic insufficiency complicating aneurysm of the ascending aorta, the diastolic murmur is clearly audible along the right sternal border, whereas in valvular aortic insufficiency it is best heard along the left sternal border. As a result of this peculiar conduction the diastolic murmur in aneurysm of the aorta is audible in the fourth intercostal space at the right sternal border while in valvular aortic insufficiency it is heard at the left sternal border.

The final diagnosis is established only after isotope and X-ray examination. If the aneurysm does not contain a large parietal thrombus its shadow, in distinction from shadows of tumours found in the mediastinum, always pulsates. Isotope scintigraphy demonstrates the size and shape of the aneurysm which is easily distinguished from tumours of the mediastinum. Contrast study of the aorta is only recommended for patients chosen for surgical treatment of the aneurysm. The size and shape of the aneurysm, the state of the afferent and efferent aortic areas, the presence of a parietal thrombus, and the condition of organs adjacent to the aneurysm are determined from the aortogram. The differential diagnosis of aneurysm of the thoracic aorta not attended by intolerable pain is discussed in the chapter 'Pneumonia'.

Diseases of the Lungs

Acute intolerable chest pain is caused by stimulation of the parietal pleura. It is a particularly constant occurrence in pneumothorax and fibrinous pleurisy. Pneumomediastinitis may also be included in this group of maladies because diseases of the lungs are its most common cause.

Pneumothorax usually begins with sudden pain in the right or left half of the chest. The severity of the concomitant dyspnoea varies sharply from case to case. We encountered patients with a small pneumothorax who had no complaints and who could not determine

the time when it had occurred. The correct diagnosis was only made after X-ray examination. In the remaining cases the development of pneumothorax was attended by sudden unilateral pain and dyspnoea which appeared at rest, during cough or physical exertion, e.g. in labour or on straining at stool. There is no room for doubt that the most common cause is severe attack of paroxysmal cough which leads to a twentyfold increase in intrabronchial pressure.

Air enters the pleural cavity through the rupture in the parietal or visceral pleura. The internist is most frequently faced with spontaneous pneumothorax which is favourable in most cases and terminates in the disappearance of the air in three to five weeks. Valvular pneumothorax is rare and marked by progressive intensification of pain and dyspnoea. The pressure of air in the pleural cavity may exceed atmospheric pressure. The resulting displacement of the mediastinal organs causes life-threatening symptoms.

The clinical picture of pneumothorax may be very vivid, in which case no difficulty arises for making the diagnosis. Unfortunately, the typical clinical picture of pneumothorax was encountered in our practice much less frequently than a picture poor in symptoms. It is quite possible that this is why we fully agree with Hegglin (1961) who claims that it is often very difficult to establish the diagnosis of pneumothorax clinically.

There are obviously fewer diagnostic difficulties when the 'three major' signs of pneumothorax (pain in the chest, dyspnoea, tachycardia) appear after injury, gastroscopy, thoracocentesis, pericardocentesis, aspiration biopsy of the liver, and block of the stellate ganglion or brachial plexus. It is far more difficult to make the diagnosis of spontaneous pneumothorax occurring, it would seem, in the prime of health, often in the middle-aged.

A sudden onset, acute chest pain, dyspnoea, often severe, and tachycardia are also often encountered at the beginning of myocardial infarction. A patient with suspected myocardial infarction is examined in bed and the diminished respiratory excursion of the involved side of the chest characteristic of pneumothorax is therefore unnoticed. The tympanic shade of the percussion sound in a small pneumothorax is usually unclear.

The correct diagnosis is easily made by means of radioscopy or radiography, because these methods easily demonstrate even relatively small amounts of air in the pleural cavity. Negative results of examination (absence of dynamics in ECG changes and normal activity of transferase in blood serum) are of no less diagnostic significance.

Acute intolerable chest pain in **emphysema of the mediastinum** in many respects resembles pain in extensive myocardial infarction. We have not always been successful in identifying the cause of mediastinal emphysema, although the diagnosis seemed obvious since

it was verified by the appearance of subcutaneous crepitation on the neck and upper chest. X-ray revealed free air in the mediastinum in such cases. Air bubbles on the periphery of the heart and lungs sometimes form a peculiar light corona around them.

Careful scrutiny of the medical history made it possible in most cases to link the pneumomediastinum with rupture of some air-containing organ (trachea, bronchi, oesophagus). In some cases emphysema of the mediastinum developed simultaneously with pneumothorax and we managed to disclose their cause only after a long period of comprehensive study of the patient. Emphysema of the mediastinum was distinguished from myocardial infarction on the basis of the results of clinical examination in most cases.

Dry pleurisy is usually one of the signs of some pulmonary disease or multisystemic lesions. In some cases it is simply the first manifestation of these diseases, in others, their mild form. The severity of chest pain in dry pleurisy may sharply differ from case to case.

In severe cases the patient is obliged to lie on the affected side or sit up in bed. Movements are stiff, because any movement sharply intensifies the pain; the pain is mostly of a stabbing character. Breathing is shallow. If the patient should only take a deeper breath, the pain is sharply intensified.

Excursions of the chest are diminished, which is particularly noticeable on the affected side. A characteristic pleural friction rub is heard on auscultation. Diminution of respiratory movements of the lungs is often marked by the formation of disk-like atelectases. Movements of the diaphragm on the affected side are restricted.

Chest pain usually appears two to five days before the pleural friction rub. Body temperature is often normal in dry pleurisy. Fever, if present, varies in severity and duration depending on the principal disease. If dry pleurisy is a phase of pleurisy with effusion, the pleural friction rub and the chest pain disappear with the appearance of effusion.

Pain in the chest is sharpest in **pleurodynia** (epidemic myalgia) which is caused by Coxsackie viruses. Chest pain in this disease precedes the pleural friction rub by three to seven days and is experienced for one or two weeks. It is usually localized in the lower thorax along the diaphragm. Such diaphragmatic pleurisy is a diagnostic problem because there is no characteristic pleural friction rub. Pain is often referred to the abdomen.

Chest pain in the **periodical disease** (familial Mediterranean fever) appears a few days prior to the fever and lasts for several days. Careful X-ray control reveals a small amount of effusion in the pleural cavity usually in one of the costodiaphragmatic sinuses.

Fever lasts a few hours or days. The attacks of chest pain in periodical disease usually recur at definite time intervals. They develop stereotypically. Occasional attacks differ one from the other only

in the intensity, spread and duration of the pains. The diagnosis is easier to make if the patient's nationality is known and if the chest pains are accompanied by other manifestations of periodical disease.

Dry pleurisy in **Dressler's syndrome** usually proves to be merely the first phase of pleurisy with effusion. Simultaneous development of signs of dry pericarditis or pericarditis with effusion and pneumonia makes it much easier to recognize the disease. In systemic diseases and tumours dry pleurisy causes no severe chest pain. It is never the principal sign of the disease.

Supplement VI-1

Causes of Protracted and Recurring Chest Pain

I. Cardialgia
  1. Angina pectoris.
  2. Non-coronarogenic cardialgia.
     Neurocirculatory dystonia.
     Climacteric cardiopathy.
     Mitral valve prolapse.
     Myocarditis and cardiomyopathy.
     Rheumatic carditis.
     Aortalgia.

II. Diseases of other chest organs.
     Diseases of the lungs and pleura.
     Diseases of the mediastinal organs.
     Diseases of the diaphragm.

III. Diseases of the chest wall.
  1. Lesions of the intercostal nerves.
     Herpes zoster.
     Intercostal neuralgia.
     Slipping costal cartilage syndrome.
  2. Affection of the muscles of the chest and upper limbs.
     Smaller pectoral muscle syndrome.
     Fibromyositis.
     Scalenus anticus syndrome.
     Reflex dystrophy of the upper limb (shoulder-hand syndrome).
  3. Diseases of the bones and joints.
     Cervical osteochondrosis.
     Tietze's syndrome.
     Manubrio-sternal syndrome.
     Xiphoidalgia.
  4. Other diseases.
     Diseases of the mammary gland.
     Mondor's disease.

Supplement VI-2

Causes of Acute Intolerable Chest Pain

I. Diseases of the heart.
  1. Myocardial infarction.

2. Pericarditis.
3. Myocarditis and cardiomyopathy.

II. Diseases of the aorta.
1. Dissecting aneurysm of the aorta.
Dissecting aneurysm of the ascending aorta.
Dissecting aneurysm of the descending aorta.
2. Rupture of aneurysm of the thoracic aorta.
Traumatic (false) aneurysm of the aorta.
Congenital aneurysm of the thoracic aorta.
Acquired aneurysm of the thoracic aorta.
3. Aneurysm of the thoracic aorta with compression of the adjacent organs.

III. Diseases of the lungs
1. Pneumothorax and pneumomediastinitis.
2. Dry pleurisy.
3. Epidemic myalgia.
4. Periodical disease.

Chapter VII

Constipation

Constipation is a clinical syndrome manifested by the retention of faeces in the rectum the evacuation of which is difficult, in most cases, and occurs at intervals longer than those of a healthy individual.

Examination of large numbers of healthy persons from all walks of life showed that in more than half of them the intestine is evacuated once a day. The passing of stool twice a day or three times in two days is encountered somewhat less frequently. The stool is passed less than once a day in only 5 to 9 per cent of healthy young and middle-aged individuals. Even very rare stools are quite compatible with good health. If a patient complains of constipation and a feeling of incomplete evacuation of the rectum during defaecation, the physician must always perform digital examination of the rectum because this sensation may be caused by mild prolapse of the mucous membrane, usually of the anterior part of the rectum, into the anus or by a disease of the perineal muscles.

On being retained in the rectum the faeces become gradually harder and when passing through the anal canal often injure its mucous membrane. Haemorrhoids, anal fissures, ulcers, and anusitis are frequent causes of not only constipation but of complications too. Constipation is sometimes attended by the formation of coproliths in the rectum or colon. Pressure exerted by these stones on the intestinal wall may cause the formation of ulcers, the perforation of which results in peritonitis. Mechanical stimulation of the intestinal wall often gives rise to reflex pains in the sacrum, buttocks, posterior surface of the thighs, and in the hip joints. Tachycardia and dizziness develop sometimes and abate after the stool is passed.

Patients suffering from constipation often complain of easy fatiguability, an unpleasant taste in the mouth, nausea and anorexia. Their tongue is often coated and the abdomen distended. Persons with chronic constipation often have a sickly yellowish skin with a brown hue. A few months after constipation is corrected, the face becomes normal in colour. Patients with constipation often have marked anaemia and signs of vitamin deficiency. Their development is attributed to disorders of absorption of the nutrients under the effect of purgatives which are usually taken in such cases.

The classifications of constipation suggested by Smotrov (1934), Pevzner (1940), Lorie (1957) and Gukasyan (1959) are especially

popular in the Soviet Union. All these classifications are unfortunately extremely far removed both from contemporary knowledge of rectal physiology and from the requirement of the differential diagnosis of this syndrome. The classification which we use was developed with due consideration for the differential diagnosis of internal diseases (Supplement VII-1).

The forms of constipation encountered by the practitioner are the consequence of either congenital or acquired diseases and are one of the commonly found syndromes of these diseases, or syndromes that are constantly in attendance. Besides these secondary forms of constipation, which are often symptomatic in essence, the modern clinic distinguishes constipation of an unrecognized cause which is possibly induced by functional disorders of peristalsis and the act of defaecation. Anglo-American authors call these forms simple constipation. Gukasyan (1959) believes that some of these forms of constipation are of conditional-reflex origin.

The classification of constipation we use in practice has, no doubt, its shortcomings, but it meets the requirements of practical medicine, because it emphasizes the firm association of most forms of chronic constipation with a definite number of congenital and acquired diseases of the internal organs and nervous system and with metabolic diseases. It is easily used for the purpose of both differential diagnosis and for planning treatment.

Constipation in Normal Size of the Large Intestine

Simple colonostasis (simple constipation). A healthy person on a meat and vegetable diet passes the stool much less frequently, while a person on a vegetable diet defaecates two to three times a day. A patient with colonostasis on the same diets passes the stool irregularly and much less frequently than a healthy individual; the faeces are harder than those of a healthy person and are passed with difficulty and often with pain. The large intestine is normal in size. The patient's general condition is satisfactory.

Two groups of causes of simple colonostasis may be distinguished. Some causes depend entirely on the patient himself while others stem mainly from unfavourable circumstances in which the person finds himself.

The role of subjective causes is determined by the factors of modern civilization. The diet of modern man consists of refined foodstuffs. It is far too mild and very poor in coarse foods. The very important role of this factor in the origin of constipation was emphasized time and again by Smotrov (1934) and other Soviet clinicians.

The role of the alimentary factor in the origin of simple colonostasis becomes obvious from the following comparison. A diet consisting mainly of maize leads to two or three defaecations daily. An artificial chemical diet composed entirely of water-dissolved substances elaborated purposefully for spacefliers results in the stool being passed once in five to seven days. The role of the dietetic factor in the origin of constipation is particularly important for elderly and old persons who, because of the inadequate condition of their teeth, prefer ground food containing no vegetable tissues.

Insufficient amounts of liquids also facilitate constipation. The role of this factor is obvious even in young soldiers and tourists who suffer constipation for some time after sweating profusely during exhausting marches on hot days. Physical activity noticeably intensifies the propulsive peristalsis of the colon. A sedentary mode of life is conducive to colonostasis.

Gukasyan (1959) points to the connection of simple colonostasis with inhibition of conditioned reflexes to defaecation. In some cases this occurs under the effect of subjective factors, in others under the effect of the environment. Quite often both these causes act simultaneously. For instance, children and adults getting up late in the morning are obliged to go to school or work immediately after breakfast. The activity of the gastrocolic reflex in such cases is not accompanied by the act of defaecation. The faeces enter the rectum and stay there, keeping it distended sometimes for a long time. Moreover, the antiperistalsis waves may force the faeces back into the sigmoid colon or the descending colon. They are compacted there which may make their passage through the anal canal difficult.

If the person again ignores the urge to defaecate, the rectal receptors no longer react to the usual stimuli. Their stimulation and, consequently, the urge to defaecate occur only under the effect of intraintestinal pressure that is higher than normal. The peristalsis waves of the usual propulsive force can no longer induce the urge to defaecate or to begin the act of defaecation. Disorders of normal motor activity of the large intestine are conducive to colonostasis.

On summing up all that has been stated it may be concluded that the main causes of simple colonostasis are inobservance of dietary hygiene, insufficient physical activity, and suppressed activity of reflex mechanisms accomplishing the act of defaecation. The diagnosis of simple colonostasis, or simple constipation, may be established only in patients with a normal size of the large intestine. In appraising the diagnostic significance of this last criterion it must be borne in mind that distension of the colon rules out the diagnosis of simple constipation, while a normal size of this intestine simply does not contradict the diagnosis but at the same time does not verify it.

This stipulation carries very important differential diagnostic significance. In many forms of constipation mentioned below, the large intestine becomes distended only some time after the disease develops. Even constipation in congenital diseases may exist for some time if the large intestine is of normal size. The diagnosis of simple constipation may therefore be made only when the colon is of normal size and only after all other causes of chronic constipation described below have been ruled out.

Constipation in Distension of the Large Intestine

Congenital aganglionosis of the colon. Constipation and even obstruction of the colon are encountered in newborns in many diseases. In most cases they are caused by congenital diseases, cerebral haemorrhage, shock, sepsis and hypoxia. Meconium is discharged from a healthy infant within the first 24 hours. Constipation of several days leads to repeated vomiting and abdominal distension. If meconium is discharged during digital examination of the rectum, it is considered that constipation and functional intestinal obstruction are most probably associated with aganglionosis of the colon.

This disease was first described in the 17th century. In 1886 a Danish clinician Hirschsprung demonstrated the results of his observations of two sick children to the Berlin Society of Paediatricians. One boy died at the age of seven months and the other at the age of eleven months; they both had a large abdomen and partial intestinal obstruction from birth. Hirschsprung was the first to point to the connection of chronic constipation with dilatation of the colon and hypertrophy of its wall. It has now been established that the disease described by Hirschsprung is caused by congenital aganglionosis, which in mild cases occurs only in the rectum, while in severer cases it spreads to part or even the entire colon. Dilatation of the intestine is always attended by its general elongation and by thickening of its wall; an intestine enlarged in all its dimensions was designated 'megacolon'.

The severity of the clinical picture of Hirschsprung's disease is determined by the length of the aganglionic segment of the large intestine. In mild cases of the disease, particularly among breast-fed infants, the normal soft faeces pass easily through the short aganglionic segment. More severe cases are marked by constipation, the degree of which is determined by the length of the affected intestinal segment and the consistency of the faeces passing along it. In some cases persistent constipation begins only after the age of 10.

At first it is mistaken for simple constipation because colonostasis is successfully treated with enemas. Constipation gradually becomes more and more persistent and the classical signs of the disease (a large abdomen, vomiting) develop. In spontaneous defaecation, the faeces are discharged in the form of a thin cylinder in a volume far below normal.

The large intestine proximal to the aganglionic segment is gradually overfilled with faeces, becomes dilated and is palpated in the left ileal region as a thick cylinder. Intensification of its peristalsis may be easily detected by auscultation or even by inspection. The abdomen is obviously distended and its skin is thin and shiny. In graver cases the stool is passed once in several days, usually only after an enema or purgatives. Vomiting and partial intestinal obstruction sometimes occur and loss of body weight and anaemia are found as a rule.

Digital examination shows normal tonus of the anal sphincter. The ampulla of the rectum is empty or contains small faecal lumps the size of a pea. Colonoscopy shows that the size of the distal colonic segment and its mucous membrane are normal. The colonoscope or rectoscope passes freely into the dilated part of the large intestine. The mucosa of this segment is thickened, hyperaemic and often has small usually superficial ulcers. A barium enema shows normal diameter of the distal segment of the large intestine and considerable dilatation of its proximal segment. Biopsy of the intestinal wall is performed in doubtful cases. Absence of ganglionic cells in Auerbach's plexus of the distal intestinal segment is a pathognomonic sign of Hirschsprung's disease.

Long-term stasis of faeces in the large intestine proximal to its aganglionic segment is complicated with time by the formation of coproliths. Pressure exerted by them on the intestinal wall leads to the formation of ulcers. In most cases these ulcers are superficial but from time to time they are complicated by haemorrhage or intestinal perforation. Enterocolitis (diarrhoea with fever, vomiting and still greater abdominal distension) is among the rare complications.

Hirschsprung's disease may be suspected in every patient who has constipation from childhood. This suspicion is regarded as substantiated if, at the time of constipation, faeces are palpated in a distended abdomen while the rectum is free of them. The final diagnosis is established from the results of biopsy.

Achalasia of the rectum. Drastic narrowing of the distal rectal segment, like drastic narrowing of the terminal part of the oesophagus, is called 'achalasia'. The clinical picture of this developmental anomaly does not differ from the picture of aganglionosis of the colon. The carriers of this anomaly have persistent constipation from infancy. Accumulation of a large amount of faeces

before the constricted rectal segment leads to dilatation of the proximal segments of the rectum.

Simultaneous drastically marked dilatation of the colon is accompanied by considerable abdominal distention. Long-term stasis of faeces is often complicated by the formation of coproliths which, in turn, may lead to the formation of stercoral ulcers and even to perforation of the intestine and peritonitis. From time to time the disease is complicated by partial intestinal obstruction. Digital examination of the rectum reveals signs identical with those in aganglionosis of the colon.

The rectum is sometimes constricted only for a distance of 2 to 5 cm in its most distal part. In such cases the constricted area and the part continuous with the healthy segment are localized in the true pelvis and cannot be found by routine X-ray examination. This anomaly is usually diagnosed by testing the response of the internal sphincter to stretching of the rectum or the sensitivity of the rectum to acetylcholine and its analogues.

The tonus of the internal sphincter in a healthy person diminishes sharply when the rectum is stretched, whereas in a patient with aganglionosis of the colon and achalasia of the rectum it increases. Parenteral acetylcholine injection causes relaxation of the normally innervated colon. Acetylcholine injection produces no effect on the pressure level within the intestinal segment devoid of ganglionic cells.

In a patient with achalasia, the wall of the stenosed rectal segment contains a normal number of ganglionic cells. With regard to function, however, this segment resembles, in all respects, an intestine devoid of ganglionic cells. Following acetylcholine injection, peristalsis and pressure in this part of the intestine do not change. The tonus of the internal sphincter in these patients increases when the rectum is stretched. The clinical picture of aganglionosis of the colon is identical to that of achalasia of the rectum and they may be distinguished from each other only from the results of biopsy.

Abnormal Rectal Dilatation Syndrome

Stretching of the rectum in a healthy person is attended by an urge to pass a stool. In some patients with constipation the sensitivity of the rectal receptors to stretching is drastically diminished. The urge to defaecate occurs only with an increase in intra-intestinal pressure, which is much higher than that in healthy individuals. This circumstance leads to the accumulation of copious amounts of faeces in the rectum of these patients. Despite the overfilled rectum, they rarely have an urge to pass the stool.

The rectum of these patients is drastically stretched along its entire length beginning from the anal canal. Its anatomical structure is normal. Simultaneous dilatation of the rectum and distal part of the sigmoid colon is encountered in rare cases. A reduced sensitivity of the rectum to stretching is combined in some patients with relaxation of the muscle tonus of its sphincter. Examination sometimes reveals a gaping sphincter usually with irritation of the perineal skin by faeces discharged from the anus.

The surgical treatment of constipation in patients with the abnormal rectal dilatation syndrome is regarded to be contraindicated. Non-operative methods usually produce good results and the rectum diameter even diminishes. It is vitally important to distinguish constipation in the abnormal rectal dilatation syndrome from constipation in congenital diseases of the intestine described above and from mechanical constipation which yields only to surgery. The differential diagnosis of these diseases is comparatively simple.

Constipation in overstretching of the rectum is usually suffered from childhood. It rarely begins from middle age. Constipation which we refer to the mechanical form usually begins in elderly and old persons.

The rectal ampulla is always empty in Hirschsprung's disease, but always overfilled with faeces in the abnormal rectal dilatation syndrome. Neither digital nor X-ray examination discloses a stricture of the rectum, which is an invariable sign in its achalasia.

In the abnormal rectal dilatation syndrome the urge to pass the stool is very weak, but not completely lost. The patient experiences this urge when the faeces enter the distal segment of the large intestine. The distal segment of the intestine in Hirschsprung's disease is always empty. That is why such patients do not have an urge to defaecate despite long-term constipation. Trial therapy beginning with the prescription of enemas is always effective in the abnormal rectal dilatation syndrome, but never in congenital constipation.

Mechanical Constipation

The propulsive activity of the rectum may be impaired by mechanical obstruction to the movements of the faeces. These obstructions may be conditionally divided into organic and functional. In the first case the movement of the faeces is hampered by a tumour of the intestinal wall, cicatricial stenosis of the intestine, drastic increase of its tonus, and obstruction of its lumen by coproliths. Movement of the faeces in the intestine is often impaired because it is compressed by ascites, an enlarged uterus or its adnexa, or tumours of other neighbouring organs. In the second case the

colonostasis is caused not by organic narrowing of the intestinal lumen, but by disorders of the reflex mechanisms of its evacuation mainly because of pain arising from the intestine itself or structures connected with it.

Tumours of the large intestine. Depending on the rate of tumour growth, the resistance to the passage of faeces along the large intestine grows slowly or rapidly. The intestine gradually dilates above the site of its stenosis and its wall thickens becauses of hypertrophy of its muscular coat, the circular muscular fibres undergoing hypertrophy much more sharply than the longitudinal fibres. With the gradual development of the clinical picture of chronic partial ileus, the outlines of the dilated intestinal segment become less and less clear and its haustration gradually becomes more marked and coarse, which is explained by hypertrophy of the intestinal wall. From time to time the disease is complicated by the picture of acute ileus.

Adenocarcinoma is the most common tumour of the large intestine. In about 40 per cent of cases it is localized in the rectum. The incidence of involvement of the sigmoid colon is half that of the rectum, while the incidence of tumours of the descending colon is half that of tumours of the sigmoid colon. Approximately 10 per cent of all adenocarcinomas are found in the ascending colon. The clinical manifestations of carcinoma of the large intestine are determined by its localization, the character of its spread, and the transverse intestinal diameter. The interaction of these factors leads to the fact that in about 25 per cent of cases constipation is the first manifestation of carcinoma of the large intestine. This is particularly characteristic of rectal carcinoma. Constipation is relatively rare in tumours of the caecum and the ascending colon. This is explained by the liquid or soft consistency of the contents rather than by the large diameter of the intestine.

The assumption that constipation is linked with carcinoma is highly probable if the constipation had appeared not very long ago in an elderly or old person. To control the constipation, the patient begins taking purgatives. The resulting diarrhoea is sometimes attributed to overdosage of the purgative. To avoid this error, the alternation of constipation and diarrhoea in an elderly or old individual should be considered an indication for thorough examination of the large intestine so as to rule out its new growth. It is essential, in such cases, to bear in mind that in the initial stages of the disease the dilatation of the intestinal segments proximal to the tumour may still be mild and that even in non-operable stages of the disease it is never as obvious as in achalasia of the rectum.

Endometriosis is encountered in 8 to 21 per cent of females of child-bearing age subjected to operation for diseases of the true pelvis. The diagnosis of endometriosis of the rectum or sigmoid colon

was made in approximately one fourth of patients. The endometrial tissue may be found on or in the intestinal wall. Sometimes it surrounds the intestine and causes its stenosis. In more than half the women, the intestinal manifestations exacerbate markedly in the menstrual or premenstrual period.

Constipation which, together with rectalgia or rectal neuralgia (proctalgia fugax), usually incapacitates the patient is a particularly frequent occurrence. Partial or even total ileus sometimes occurs. Tenesmus or diarrhoea develops during menstruation if the tumour is in the rectum. Painful micturition or pollakiuria is often encountered simultaneously with pain in the lower abdomen and rectum. Dysmenorrhoea and sterility develop in more than half the females.

Physical examination usually discloses enlargement of the uterus and of one or both adnexa. In metastasis of a tumour to the rectum, elastic mildly tender nodes are palpated on its anterior wall. Proctoscopy and X-ray demonstrate a tumour projecting into the lumen of the large intestine and obstructing it. The intestinal mucous membrane above the tumour has a normal appearance.

Repeated examination of the patient convinces one that the tumour changes in size regularly. It grows larger during menstruation and is smaller in the period between menstruations. The results of clinical examinations allow a tentative diagnosis of endometriosis to be made.

X-ray usually shows a filling defect in the large intestine and dilated area of the intestine proximal to the defect. The mucous membrane above the site of the lesion appears normal. Owing to this, endometriosis can be differentiated from carcinoma of the large intestine which is characterized by impaired intactness of the mucosa, as a result of which its outlines on the radiograph lose their regular and linear character. The findings of X-ray do not allow one to rule out the possibility of the intestine being compressed by an adjacent enlarged lymph node or tumour of an abdominal organ.

Diverticulosis of the large intestine. In carcinoma of the large intestine, constipation is often combined with abdominal pain experienced soon after meals. The pain is most likely caused by increased peristalsis of the large intestine under the effect of a gastrocolic reflex. Such types of pains combined with constipation are often also encountered in diverticulum of the large intestine which at elderly and old age is mostly found in the sigmoid colon. Carcinoma and diverticulosis of the large intestine may exist simultaneously in one patient. The differential diagnosis between them may only be made after comprehensive examination including exploratory laparotomy.

A record of the degree to which the following symptoms are pronounced may be of immense help in discussing the causes of the

ailment. The appearance of constipation in an elderly or old individual who previously had a normal rhythm of defaecation is characteristic of carcinoma of the large intestine. Constipation is often encountered in diverticulitis of the large intestine, but it has become habitual to the patient as he had been troubled with it over the years. A sensation of incomplete evacuation of the rectum is often encountered in carcinoma. There are no such sensations in diverticulosis. Diverticulosis of the large intestine can be complicated by intestinal haemorrhage, which is sometimes copious. Bleeding in carcinoma is a constant occurrence, but it is negligible.

Periodical exacerbations of the disease with the appearance of abdominal pain in combination with fever, leucocytosis, nausea and vomiting are often encountered in diverticulitis. Carcinoma of the large intestine is marked only by a progressive course in all cases. Fever, leucocytosis and repeated vomiting in carcinoma are always combined with anaemia and loss of body weight. They appear only in the late stages of the disease.

X-ray may demonstrate a filling defect in the intestine in both diseases; in diverticulosis, the length of the defect is usually considerable, whereas in the initial stages of carcinoma it is usually no longer than 3 to 5 cm and is clearly outlined. The results of colonoscopy with spot biopsy may be of great value in the differential diagnosis between these two diseases. When the area of the large intestine is inaccessible for visual inspection, exploratory laparotomy is the only method for identifying the cause of the disease.

Coprostasis on the right side. Smotrov (1934) claims that segmental inflammatory processes in the left half of the large intestine are sometimes complicated by reflex contralateral coprostasis. The content of the caecum and ascending colon in a healthy person is loose or soft in consistency. The faeces may sometimes be retained for a very long time in this segment of the large intestine.

Continuous absorption of water leads to gradual thickening of the loose and soft contents of the right part of the colon. This process terminates in the formation of hard faecal matter and sometimes coproliths which may be easily palpated in the right ileal region. In contrast to a tumour, they are painless and easily movable on palpation.

The use of a radiocapsule confirms to some measure Smotrov's assumption on the possibility of reflex coprostasis. Prolonged spasm of the descending colon in mucous colic (the string sign) sharply delays passage of the radiocapsule through the proximal segments of the large intestine. Constipation is a very frequent finding in this syndrome, but the principal sign is pain, as a rule.

Coproliths. Delayed passage of the intestinal contents and intensified absorption of water lead to the formation of hard faeces. Remaining for a long time in the intestine, they are covered with

mucus and, under the effect of peristalsis, become smooth and rounded resembling bile stones in appearance. The distal part of the rectum is the site of 98 per cent of all caproliths. In old persons and children they are sometimes seen through the stretched anus.

Though they are the consequences of constipation, the coproliths, once formed, always intensify it noticeably. The parts of the large intestine proximal to the coproliths grow noticeably in diameter and their muscular coat is hypertrophied. Megacolon develops gradually, which is sometimes complicated by intestinal obstruction. The coproliths are clearly demonstrated on radiographs. Their detection and removal is an indispensable condition for successful treatment of constipation, particularly in the aged.

Stricture of the large intestine. Many diseases of the large intestine are marked by the formation of ulcers, the cicatrization of which sometimes results in the formation of strictures. The lumen of the large intestine may also be narrowed in cicatrization of the adjacent connective tissue. Strictures form particularly often in cicatrization of tissues after traumatic injuries and in cicatrization of non-specific ulcers of the large intestine and perineum, after healing of rectal and pararectal abscesses, and after operations on the muscles of the perineum and organs of the true pelvis. X-ray therapy in diseases of these organs sometimes leads to the development of inflammatory lesions in the sigmoid colon and rectum. Scarring of these lesions is attended by the formation of strictures which prevent movement of the faeces along the large intestine. The intestine proximal to the stricture becomes dilated and its muscular coat hypertrophied. Constipation is the end functional result of these morphological changes in the large intestine. The persistence of constipation and the pronounced character of the dilatation of the large intestine are determined by the extent of the stricture and the rate of its development.

Ptosis of the perineum and prolapse of the rectal mucosa, haemorrhoids. In the act of defaecation the anus of a healthy person descends to a level determined by a line drawn from the pubic symphysis to the coccyx. In many patients suffering from constipation the anus descends much below this level when straining in defaecation. In ptosis of the perineum the anterior rectal wall prolapses into the upper part of the anal canal and produces a sensation of its incomplete evacuation. To evacuate the canal completely, the patient strains, but the more he strains, the further the mucous membrane moves and intensifies the feeling of incomplete evacuation. Active defaecation becomes difficult because the muscles elevating the anus are weakened and the reflex defaecation mechanisms are impaired.

Prolapse of the rectal mucosa is often combined with haemorrhoids. Inflammation of the haemorrhoids and the accompanying

pain make defaecation still more difficult. So as not to suffer this pain, the patient suppresses the urge to defaecate either intentionally or subconsciously. A vicious circle is thus created. The longer the faeces are retained in the rectum, the harder they become and the more painful is defaecation. The diagnosis of this cause of constipation is made from the information gained by questioning the patient about his sensations during defaecation and from the results of the inspection of the perineum and digital examination of the rectum. If there are no inflammatory phenomena, the tonus of the anal sphincter is normal or weakened and hard faecal matter is found in the rectal ampulla.

Fissure of the anal canal, cryptitis, papillitis, proctalgia fugax, tabes dorsalis. Constipation in the elderly and aged is caused by such diseases of the anorectal region as haemorrhoids, fissures and ulcers of the anal canal, cryptitis and papillitis.

The act of defaecation in patients with fissure of the anal canal is accompanied by sharp, lancinating pain in the anus. The faeces often contain a small admixture of blood or only spots of blood are seen on the toilet paper. Digital examination reveals spasm of the sphincter. Introduction of the finger into the anal canal is painful. The wall of the anal canal around the fissure or ulcer is often thickened and tender. The disease is frequently complicated by itching in the anus and the formation of perianal abscesses. Anal fissures and ulcers often prove to be among the complications of ulcerative colitis and Crohn's disease. They may also be encountered in rectoanal localization of syphilis, tuberculosis, and carcinoma.

Constipation arises from and is sustained by intentional or spontaneous suppression of the urge to pass the stool. The main cause of this is painful defaecation. Constipation in cryptitis and papillitis is of exactly the same origin. The obstruction of the draining ducts of the anal glands in cryptitis may be complicated by the formation of a perianal abscess. Defaecation noticeably intensifies the pain in the perineum.

The act of defaecation also makes the usually moderate pain syndrome in papillitis much more severe. In papillitis of long duration this leads to the development of constipation with attendant dilatation of the large intestine. Intentional or spontaneous suppression of the urge to defaecate is also encountered in proctalgia fugax and tabetic crises. The first of these diseases is marked by spasm of the anal sphincter, whereas in the second disease the tonus of the anal sphincter is usually reduced.

Psychogenic and Neurogenic Constipation

Many psychic diseases are complicated by colonostasis. Constipation develops in middle age, as a rule. In rare cases it begins

from childhood. It is an especially frequent occurrence in states of depression, schizophrenia and nervous anorexia. Patients with these diseases often ignore the urge to defaecate. It is possible that these urges are noticeably diminished under the effect of the disease. Colonostasis progresses gradually and the stool is passed less and less frequently. A spontaneous stool may not be passed for one or two weeks.

Constipation is sometimes the first complaint with which these patients come to a physician. Its true cause is not always obvious. Besides constipation, these patients suffer from impaired rhythm of sleep, increased irritability, sweating and anorexia, and they are incapable of mental concentration on a subject being discussed. Successful treatment of the principal disease relieves constipation.

According to Gukasyan's (1959) experience 'some patients with chronic constipation are preoccupied with their stool without end, elaborating their observations with thorough detail'. They are extremely alarmed if the stool is delayed and often take purgatives to regulate it. The retention of stool which usually occurs in the days following medication with the purgative causes them much suffering. The daily passage of the stool becomes an absolute ritual of their life. They achieve this by taking purgatives frequently. Constipation in these patients is gradually replaced by diarrhoea.

The loss of fluids and electrolytes, potassium in particular, is attended by apathy, weakness and abdominal distension. The skin loses elasticity. The large intestine gradually loses haustration and becomes dilated; its mucous membrane often acquires a black colour. Deep strangulations appear on some of the segments and are sometimes mistaken for strictures. Steatorrhoea develops in simultaneous involvement of the small intestine. Severer cases are marked by hypokaliaemic paralyses, a marked thirst, and increase in blood residual nitrogen. In the long run the intestine loses its water-absorption capacity and permanent diarrhoea sets in.

The formation of pseudostrictures and dilatation of the entire large intestine, its right segments in particular, are characteristic diagnostic signs of the abuse of purgatives. In these patients, constipation appears at young and middle age and is usually not over-persistent. The formation of pseudostrictures of the large intestine is a pathognomonic sign of the disease.

Affections of the lumbosacral part of the spinal cord and the cauda equina (e.g. tumours, syphilis) are attended by severe colonostasis. The large intestine is sharply dilated by the faeces accumulating in it. It often takes a radiocapsule more than three weeks to pass along it.

Metabolic, Endocrine and Toxic Constipation

Constipation is encountered constantly in some endocrine diseases and frequently in others. Colonostasis is often among the earliest signs of myxoedema. The other signs of this disease (coarsening and hard oedema of the skin developing under the effect of disturbed mucopolysaccharide metabolism, bradycardia, characteristic changes of the face, voice and hair) usually appear later than constipation. Progressing gradually, constipation becomes more persistent and leads to dilatation of the large intestine. The final diagnosis is made from the results of biochemical and radioisotope examination of thyroid function.

Constipation is observed particularly often during pregnancy. Forceful straining during defaecation intensifies haemorrhoids which are found in a mild state in most pregnant women. Constipation is quite frequently complicated by fissures of the anal canal. According to contemporary conceptions, the main role in the development of constipation is played by the metabolites of progesterone, the secretion of which is sharply increased with the onset of pregnancy. In the later stages of pregnancy, insufficient physical activity and compression of the sigmoid colon by the enlarged uterus predispose to constipation.

Colonostasis is often encountered in patients with diabetes mellitus complicated by neuropathy. Constipation is usually moderate but sometimes it is very persistent and attended by dilatation of the large intestine.

Severe constipation with vomiting and colicky pains in the abdomen often predominates in the clinical picture of acute intermittent porphyria and lead poisoning. Signs of peripheral polyneuritis appear in these patients with time. In taking the medical history of a patient with constipation it is always essential to clarify its possible connection with the use of drugs often inducing exacerbation of porphyria or a possible contact of the patient with lead. The association of constipation with lead poisoning must be verified by a high content of lead in the blood or its increased excretion in the urine and the detection of red cell basophil granulation. The association of constipation with porphyria must be confirmed by revealing an increased content of porphyrin or its colourless precursor porphobilinogen in urine.

Persistent constipation with marked dilatation of the large intestine often develops in regular administration of drugs. Colonostasis with dilatation of the large intestine is always encountered in long-term medication with hypotensive agents (e.g. hexamethonium), anticholinergic agents (e.g. atropine and its analogues) and

monoamine oxidase inhibitors. Moderate constipation develops frequently in patients who regularly take diuretics, soporifics, sedatives, antidepressants, preparations of iron and calcium carbonate.

The importance of drugs in the origin of constipation is often overestimated. Drug constipation is rapidly relieved as a rule after the agent causing it is discontinued. Constipation in patients with severe heart failure usually disappears soon after oedema is relieved. Diuretics noticeably intensify constipation in patients with congestive heart failure by causing hypokaliaemia. Correction of hypokaliaemia but with persisting heart failure only brings some relief from constipation but does not eliminate it completely.

Muscular Constipation

The passage of faeces along the large intestine is accomplished by the coordinated activity of the muscles of the large intestine and abdominal cavity, and every form of constipation is therefore muscular. The term 'muscular constipation' used as the title designates a group of constipation forms which are mainly consequent upon weakness of muscles responsible for movement of the faeces and their discharge from the intestine.

A sharp increase in intra-abdominal pressure during defaecation is mainly achieved by contraction of the diaphragm. The functional state of the diaphragm suffers noticeably in diseases of the lungs, particularly in old persons (obstructive and senile pulmonary emphysema), and in psychic diseases. The muscles of the abdominal wall which also play an important role in raising intra-abdominal pressure are often weakened in adiposity, frequent pregnancies, ascites and tumours of the intra-abdominal organs. Contraction of the muscle elevating the anus is very important in the discharge of faeces from the rectum. This muscle is often atrophied in females who have given birth to many infants. Functional deficiency of this muscle is evidently among the causes of constipation in these women.

Atrophy of the rectal smooth muscles is one of the main manifestations of scleroderma and Chagas' disease. The latter is not encountered in the Soviet Union and is therefore not discussed in this book. The gastro-intestinal tract is involved from the early stages of scleroderma. The muscle tissue of the oesophagus and the large intestine is replaced by connective tissue. Movement of the faeces in the large intestine is drastically delayed, often leading to constipation and sometimes to the development of the clinical picture of ileus. Constipation in congenital myotonia is explained by atrophy of the smooth muscles of the intestinal wall. Diminished function of the muscles of the intestinal wall is one of the causes of colonostasis in old individuals.

Constipation is often the principal and sometimes the only manifestation of the disease. Thorough examination of the patient makes it possible to identify its cause and prescribe aetiotropic treatment.

Supplement VII-1

Types of Constipation

1. Constipation in normal size of the large intestine.
   Simple colonostasis (simple constipation).
2. Constipation in dilatation of the large intestine.
   Congenital aganglionosis of the colon.
   Achalasia of the rectum.
3. Abnormal rectal dilatation syndrome.
4. Mechanical constipation.
   Tumours of the large intestine.
      Adenocarcinoma.
      Endometriosis.
   Coprostasis on the right side.
   Coproliths.
   Other lesions of the large intestine.
      Strictures of the large intestine.
      Diverticulosis.
      Ptosis of the perineum and prolapse of the rectal mucosa, haemorrhoids.
   Fissure of the anal canal, cryptitis, papillitis, proctalgia fugax, tabes dorsalis.
5. Psychogenic and neurogenic constipation.
5. Metabolic, endocrine and toxic constipation.
7. Muscular constipation.

Chapter VIII

Diarrhoea

According to Roux's classical definition, diarrhoea is a clinical condition in which the stool is looser and more frequent than ordinarily. The patient's complaints of changes in the frequency and consistency of the stool may in most cases be regarded as syndromes characteristic of affection of the small or large intestine (Supplement VIII-1).

The differential diagnosis of diarrhoea may be much simpler if the patient is thoroughly questioned. It is particularly important to clarify how frequently remissions occurred and lasted, the character of the stool, the time of the urges to defaecate, the age at which diarrhoea had begun, the effect of the disease on the patient's working capacity and body weight, the history of operations and diseases, and concomitant diseases. Nocturnal diarrhoea is almost always organic in character, whereas diarrhoea occurring in the morning may be purely functional.

In diseases of the small intestine, e.g. coeliac disease or non-tropical sprue, the absorption of nutrients, vitamins, water and electrolytes is impaired. As a result, chyme of a volume larger than ordinary enters the caecum. If the reservoir function of the large intestine is normal, the stool may be passed no more than two or three times a day. The daily and single volume and mass of the stool exceed normal by far.

A large volume of a single stool is encountered only in patients with normal function of the distal segment of the large intestine. In such cases the pathological process is localized either in the small intestine or in the proximal segment of the colon. These patients experience neither imperative urges to defaecate nor tenesmus during defaecation. Diarrhoea in involvement of the descending and sigmoid colon and rectum is characterized by a number of features among which diagnostic importance is attached to imperative and frequent need to defaecate, a small volume of a single stool, and frequent content of blood and mucus in it.

In affections of the small intestine, pain is always felt in the paraumbilical region. Affection of the caecum and ascending colon is mostly attended by pain in the right lower abdominal quadrant. The pain intensifies after meals. In affection of the distal segment of the large intestine, pain is localized in the left lower abdominal quadrant or in the sacrum. It is noticeably relieved after the stool or gases are passed.

In some cases diarrhoea alternates with constipation. This is a particularly constant occurrence in carcinoma or diverticulitis of the large intestine, functional neurogenic diarrhoea, moderate stenosis of the large intestine, diabetes, thyrotoxicosis, tabes dorsalis and abuse of purgatives. This chapter deals only with diseases in the clinical picture of which diarrhoea is the only or the predominant syndrome.

Inspection and examination of the stool considerably help in the differential diagnosis. Vegetative forms of *Entamoeba histolytica* or other protozoa may be found during microscopy of warm faeces. The causative agents of dysentery may be isolated on faecal cultures. Examination of the stool is supplemented by digital rectal examination after which X-ray of the gastro-intestinal tract is undertaken.

Survey radiograph of the abdomen reveals signs of ileus and acute dilatation of the colon. This is followed by X-ray of the large intestine and then by examination of the oesophagus, stomach and small intestine. The X-ray findings are supplemented by the results of proctosigmoidoscopy and colonoscopy with spot biopsy of two or three areas of the mucous membrane. In many cases the diagnosis may be considerably advanced by the results of aspiration biopsy of the small intestine and detailed study of the character of the disorders of digestion and absorption of the nutrients.

Gastrinoma

It was routine, in the past, to distinguish tumours according to the site of their origin and their histological structure. Now tumours are subdivided more and more frequently on a functional but not anatomical basis. Endocrine tumours are classified according to their ability to secrete this or that hormone. Gastrinoma, for instance, is the name given to a gastrin-secreting tumour. It may be found in the stomach, duodenum or pancreas.

The clinical picture of gastrinoma is very diverse. Gastric or duodenal ulcer is found in 84-92 per cent and diarrhoea in 40-83 per cent of such patients. Diarrhoea in most cases is encountered together with gastric ulcer. In 18-40 per cent of cases it is the first sign of the disease. Gastric ulcer develops later in these patients, sometimes several years after the onset of this disease. Gastrinoma may be manifested as simple or watery diarrhoea. The diagnosis of gastrinoma should be assumed not only when diarrhoea is combined with duodenal ulcer as it was pointed out by Zollinger and Ellison, but also when it is combined with hypersection of hydrochloric acid and gastric juice. It is possible that mild gastrinoma may be manifested in some cases only by a semiformed or loose stool rich in fat.

Diarrhoea in gastrinoma is directly linked with hypersecretion of hydrochloric acid. It disappears after total gastrectomy. Aspiration of hydrochloric acid through a gastric tube also leads to temporary cessation of diarrhoea. The role of gastrin in the pathogenesis of diarrhoea was clarified by infusing it intravenously into humans and animals. Intravenous infusion of pentagastrin causes a marked decrease in the absorption of sodium and water from the small intestine. Gastrin probably causes an effect on the motor and absorption functions of the stomach not directly, but through the secretion of hydrochloric acid. This is confirmed by the disappearance of diarrhoea immediately after correction of gastric juice hyperacidity even if the tumour is still not removed.

In gastrinoma the ulcers are most commonly found in the duodenum. The stomach is the second in frequency of localization. In rare cases the ulcer forms in the jejunum. The course of the ulcer may be very diverse. In some cases the ulcer in gastrinoma hardly differs from ordinary peptic ulcer. In others the pain syndrome is persistent and destructive processes prevail with rapid development of such threatening complications as perforation and haemorrhage. The ulcer is typically combined with marked gastric juice hypersecretion and with diarrhoea which precedes the ulcer in some cases and joints it in others.

In most cases of gastrinoma, the ulcer is either of an unusual localization, or there are multiple ulcers. Single ulcers are often found distal to the duodenal bulb or even in the jejunum. The results were reported of the examination of 13 patients with an unusual localization of the ulcer. A tumour was found in 11 of them and an ordinary peptic ulcer only in one. Among 12 patients with multiple ulcers nine had a tumour and only three had a peptic ulcer.

It was previously believed that the determination of gastric juice acidity makes it much easier to differentiate gastrinoma from conditions with diarrhoea and gastric ulcers of other origin. With the gradual accumulation of material it was established that both the value of basal secretion of hydrochloric acid and the value of its secretion in response to the administration of histamine and pentagastrin cannot be accepted as reliable differential diagnostic criteria. Gastric juice secretion and free hydrochloric acid debit are often the same in gastrinoma and ordinary duodenal ulcer. It should nevertheless be borne in mind that a free hydrochloric acid debit four- to tenfold its normal value is encountered only in gastrinoma.

It is much easier to make the diagnosis of gastrinoma by testing the blood gastrin concentration. The radioimmune method proves to be most convenient and accurate. The digital values depend on the method. The concentration of gastrin in blood serum of healthy patients is the same as that in patients with ordinary duodenal ulcer. In patients with gastrinoma it is approximately tenfold the

normal value. This method of differential diagnosis nonetheless has the same shortcoming as that of tests for gastric juice acidity. It was found that gastrin concentration in cases of duodenal ulcer with hypersecretion may hardly differ from the concentration in patients with a small gastrinoma.

Attempts to resolve this difficulty led to the elaboration of diagnostic tests aimed at revealing the maximum ability of the individual being tested to secrete gastrin in response to a test meal and to intravenous infusion of calcium or secretin. Following intravenous calcium infusion, the blood gastrin concentration increases manifold in patients with gastrinoma as compared to patients with duodenal ulcer. The test for gastrin concentration in blood taken on an empty stomach proves to be nonetheless valuable in making the diagnosis of gastrinoma in patients suffering from peptic ulcer with hypersecretion and in patients with peptic ulcer of the anastomosis.

Gastrinoma is encountered at any age but somewhat more frequently among males than in females. It has to be differentiated from diseases marked by hypergastrinaemia, from gastric and duodenal ulcer and from diarrhoea. It is generally known that the blood gastrin content is permanently increased in atrophic gastritis. This disease is easily differentiated from gastrinoma by determining the acidity of the gastric juice. Achlorhydria is a characteristic sign of atrophic gastritis, but is never encountered in cases with gastrinoma. The clinical picture of these two diseases is absolutely different.

It is most difficult to differentiate gastrinoma from peptic ulcer. About 75 per cent of ulcers in gastrinoma form in the small intestine, the remaining 25 per cent are found in the stomach. Gastrinoma should be suspected in every case of peptic ulcer localized distal to the duodenal bulb. This assumption is most probably true when an additional ulcer is found in the distal part of the duodenum or in the jejunum, and if the patient has steatorrhoea or diarrhoea.

To verify the diagnosis of gastrinoma in such cases it is necessary to test the basal gastric juice acidity and the degree of its changes under the effect of histamine or pentagastrin. The specific features of the course of peptic ulcer must be appraised. It is particularly important to clarify the association of its exacerbations with dietary faults and also to study the character of the daily and sometimes also the seasonal pain rhythms during the exacerbation.

Ordinary peptic ulcer is characterized by a protracted wave-like course with periods of exacerbation replaced by more or less protracted remissions. The pain syndrome in ulcer-complicating gastrinoma is distinguished by exceptional persistance. Diet therapy is usually ineffective or produces only a brief remission. The pain syndrome recurs soon after treatment is discontinued, immediately after hypersecretion of acid gastric juice is restored.

The tendency to constipation is regarded a characteristic sign of ordinary peptic ulcer with gastric juice hypersecretion. Despite the high acidity of the gastric juice, most patients with gastrinoma have steatorrhoea or even diarrhoea. Watery diarrhoea is never encountered in peptic ulcer, but is a frequent occurrence in gastrinoma.

In all cases when these differences in the clinical picture and the course of the disease are insufficiently clear, and when it is necessary to make a very precise diagnosis so as to decide on the volume of stomach resection, it is necessary to test the blood gastrin content on an empty stomach and after a calcium or secretion load. The results of these tests in combination with the peculiar course of the disease enable gastrinoma to be differentiated from peptic ulcer.

In all cases of gastrinoma, its frequent combination with affection of other endocrine glands should be taken into account. Its occurrence with a tumour of the parathyroids and with hyperplasia of Langerhans' islets is found particularly often.

Diarrhoea may be the only manifestation of gastrinoma for many years and even throughout life. In such cases gastrinoma must be distinguished from other diseases marked by diarrhoea, first and foremost from coeliac disease, diffuse reticulosarcoma of the small intestine, pancreatic cholera, and the carcinoid syndrome.

Diarrhoea in coeliac disease resembles diarrhoea in gastrinoma and occurs without abdominal pain. It disappears soon after treatment with gluten-free diet is begun. Neither a gluten-free diet nor other therapeutic measures produce a noticeable effect on the course of diarrhoea in gastrinoma. Acidity of the gastric juice is a no less important differential diagnostic sign. Hour-tension of gastric juice secretion and the free hydrochloric acid debit are reduced or normal in coeliac disease. We found these values to be slightly increased only in one of our cases with this disease.

Gastric juice hypersecretion is among the cardinal signs of gastrinoma. The combination of diarrhoea with high basal acidity and high free hydrochloric acid debit is a sign reliably distinguishing gastrinoma from coeliac disease.

Information on the medical history is also of considerable differential diagnostic value. In adults coeliac disease is usually a recurrence of a disease suffered in childhood. A follow-up of the course taken by coeliac disease over a period of life that can be reviewed can disclose the replacement of periods of exacerbation by remissions. Like other signs of gastrinoma, diarrhoea has no remissions. The detection of gastric or duodenal ulcer should always be accepted as an extremely serious indication in favour of gastrinoma. Gastric ulcer usually does not develop in patients with coeliacia.

Diarrhoea in primary diffuse tumour of the small intestine (lym-

phosarcoma, reticulosarcoma, lymphogranulomatosis), like diarrhoea in gastrinoma, is marked by abdominal pain and is actually resistant to diet and ordinary drug therapy. Gastric juice acidity was reduced or normal in all our patients suffering from these tumours of the small intestine. Hypersecretion of gastric juice and high values of its acidity are characteristic of gastrinoma but are not encountered in tumours of the small intestine.

Duodenal ulcer is sometimes the earliest manifestation of isolated lymphogranulomatosis of the duodenum and the discovery of ulcer of the small intestine does not rule out the diagnosis of the tumour. A diffuse tumour of the small intestine and gastrinoma noticeably differ in their course and this makes their differential diagnosis simpler. In clinically unconvincing cases, the diagnostic problem may be solved by testing the gastrinaemia level on an empty stomach and after tolerance tests.

A gastrinoma in the pancreas is identified by means of angiography. A positive result of angiography of the pancreas verifies the diagnosis of gastrinoma while a negative result does not rule out the diagnosis of primary tumour of the small intestine.

Pancreatic Cholera

In 1958 and again in 1974 Verner and Morrison described watery diarrhoea caused by a tumour arising from the pancreatic islets. Diarrhoea predominates in the clinical picture of the disease and is at first paroxysmal. Later the remissions disappear completely and diarrhoea becomes permanent. The stool has the appearance of diluted tea and 4 to 6 litres of it are passed daily in most cases. The body loses a great amount of electrolytes in the fluid.

The daily losses of potassium in the stool may reach 300 mEq. As a result hypokaliaemia develops under the effect of which vacuolar degeneration of the tubular epithelium occurs. The patients usually die from renal failure and azotaemia associated with dehydration and hypokaliaemia. Another characteristic feature is hypokaliaemic muscle weakness which is particularly marked in the proximal muscles of the limbs. The blood calcium content is increased in half the cases.

Achlorhydria is found in approximately 75 per cent of patients. In the remaining 25 per cent the secretion of acid gastric juice does not change. Gastric ulcer was found in none of the patients with pancreatic cholera. About half of them had reduced glucose tolerance and sometimes clinical signs of diabetes mellitus. Treatment with prednisolone in a daily dose of no less than 20 mg causes a decrease in the volume of the stool in most cases and may even result in temporary remission of diarrhoea.

In the available literature we collected information on 64 patients with pancreatic cholera. About one third of them died from renal failure. A tentative diagnosis of the disease is made on the basis of a watery diarrhoea, hypokaliaemia and hypochlorhydria or achlorhydria of the gastric juice; the final diagnosis is based on the results of trial therapy, namely, on the basis of a remission occurring after surgical removal of any tumour found in the pancreas or after removal of the distal part of the pancreas. In 35 per cent of patients who underwent operation, the tumour was malignant.

Pancreatic cholera has to be differentiated from gastrinoma and the carcinoid syndrome. Watery diarrhoea is encountered in more than half of the cases with gastrinoma. It is easier to make the differential diagnosis using the results of the gastric juice acidity test and the findings of X-ray of the stomach. Gastrinoma is often encountered together with gastric and duodenal ulcer, whereas in pancreatic cholera an ulcer never occurs. In patients with gastrinoma the volume of the gastric juice and its acidity are always increased. The respective values in pancreatic cholera are either normal or below normal.

Diarrhoea in pancreatic cholera is always watery, whereas in gastrinoma it is watery only at times. The disappearance of diarrhoea for a brief period in cases of gastrinoma is achieved by gastric juice aspiration or the prescription of large doses of anticholinergic agents; in pancreatic cholera diarrhoea is relieved with corticosteroids taken in large doses.

The daily stool volume is of no less diagnostic significance. In 75 per cent of patients with gastrinoma it is no more than 1 litre and only in 25 per cent it ranges from 1 to 3 litres. The daily excretion of fluid in mild cases of pancreatic cholera ranges from 1 to 3 litres but in most cases (83.3 per cent) it exceeds 3 litres and reaches 5 to 6 litres. Azotaemia is only encountered in pancreatic diarrhoea whereas gastro-intestinal haemorrhage and perforation of an ulcer only in gastrinoma.

Carcinoid Syndrome

Carcinoid tumours may arise in any part of the gastro-intestinal tract with the exception of the oesophagus. They are most commonly found in the vermiform process and in the ileum. The carcinoid syndrome usually develops in cases with tumours arising from the ileum and most rarely in tumours arising from the vermiform process.

Carcinoid tumours of the ileum are often multiple. The primary tumour is usually small and asymptomatic. The clinical signs of the syndrome develop only in patients with metastasis of the tu-

mour to the liver, as a rule. Carcinoid tumours of the bronchi, stomach and pancreas tend to metastasize much earlier than tumours of other organs.

With the growth of the tumour, abdominal pain appears, the intestinal lumen narrows and bleeding occurs from the vessels of the ulcerated mucous membrane. Intestinal stenosis may be complicated by ileus. With the gradual spread of metastasis, cachexia develops. These complications are non-specific. They are quite rare and do not differ from complications developing in other tumours of the gastro-intestinal tract. Characteristic flushes and diarrhoea are among the specific signs drawing the physician's attention precisely to the carcinoid tumour.

Flushes were encountered in 95 per cent of patients with carcinoid tumours which called for medical aid. The flush is manifested by diffuse erythema usually spreading over the skin of the face, neck and the anterior surface of the upper chest. Erythema of the skin of the entire trunk occurs in rare cases. Erythema may be hardly noticeable or vividly displayed. Sometimes it lasts only two to five minutes and disappears without a trace. If it remains longer, the skin acquires a violet hue and even becomes cyanotic at times.

In severer cases of the carcinoid syndrome, erythema persists for several hours, sometimes for days. Oedema of the periorbital subcutaneous tissue and the conjunctiva, profuse sweating, oedema of the face, tachycardia, hypotonia and diarrhoea appear at the same time as erythema. This type of flush is typical of carcinoid tumour of the bronchi. Bright red colour of the skin, either diffuse or in occasional spots, is particularly frequent in carcinoid tumour of the stomach.

The origin of a flush was previously attributed to the effect of serotonin. It was later established, however, that its content in the blood during a flush and in the intervals between flushes does not change. It is now believed that carcinoid tumour continuously secretes kallikrein. On entering the blood from time to time kallikrein reacts with kininogen which is contained in the alpha-2 globulin fraction. As the result of this interaction lysine-bradykinin (decapeptide) is produced and converts to bradykinin (nonapeptide) consumed by the tissues or destroyed by the blood plasma kininase. Vasodilatation, the underlying factor of a flush, develops under the effect of both these peptides. The role of histamine, prostaglandins and serotonin in the genesis of vasodilatation is still not clear.

Diarrhoea is encountered in 72.5-85 per cent of patients with carcinoid tumour. According to some authors, it appears long before the flushes in 32 per cent of cases, simultaneously with them in 27 per cent and is attendant to them in 16 per cent of cases. Diarrhoea without attendant flushes is encountered in 25 per cent of

patients with carcinoid tumour. The severity of diarrhoea varies greatly from one case of the disease to another. Even in the same patient the frequency and volume of the stool change noticeably with time. Diarrhoea is encountered both in carcinoid tumours of the gastro-intestinal tract and in tumours of the bronchi. Removal of a tumour localized outside the gastro-intestinal tract leads to the disappearance of diarrhoea (Waldenstrom, 1970).

The absence of regular relations between diarrhoea and flushes evidently indicates that they differ in the mechanisms of their development. There is a current tendency to link diarrhoea with intensified motor activity of the small intestine under the effect of serotonin, and to attribute flushes to the vasodilative effect mainly of kininis and histamine.

Watery diarrhoea is encountered in 91 per cent of cases. The frequency of the stool may vary considerably, its daily volume usually does not exceed 1 litre and only in rare cases reaches 3 litres. The stool is passed much less frequently in steatorrhoea than in watery diarrhoea.

Abdominal pain is encountered in diarrhoea almost always. Its appearance is attributed to ulceration of the mucous membrane of the gastro-intestinal tract, stenosis of the intestine by the tumour itself or by cicatrized connective tissue usually growing around the primary tumour. Pain in the region of the liver is associated with the formation of subcapsular necrosis.

The differential diagnosis of carcinoid tumour is extremely difficult. The primary tumour may grow in any part of the gastro-intestinal tract and is therefore often mistaken for polyps or an ordinary tumour of the stomach, small intestine or colon. No clinical signs enabling it to be distinguished from other tumours of the gastro-intestinal tract can be detected in this period of the disease. Carcinoid tumour grows very slowly. Its characteristic signs appear only after extensive metastases have occurred. In this late period of the disease, large amounts of hormones produced by the tumour enter the blood; their physiological effect is determined by the spectrum of the clinical symptoms of the malignant tumour.

Diarrhoea in some cases is the earliest and, consequently, the only manifestation of the carcinoid syndrome. If it is watery in character, it must be differentiated from diarrhoea in gastrinoma and from pancreatic cholera; if it is manifested by a liquid stool with steatorrhoea, it must be distinguished from diarrhoea in coeliac disease and in diffuse tumours of the small intestine. The extra-intestinal manifestations of the carcinoid syndrome make the differential diagnosis between these diseases much easier.

As it was indicated above, carcinoid tumour secretes many pharmacologically active substances into the blood among which serotonin is most active. The products of its oxidation are excreted in

the urine as 5-hydroxyindolacetic acid. The daily excretion of this acid in the carcinoid syndrome is determined by the size of the tumour. It nearly always exceeds 30 mg and sometimes reaches 1000 mg. In interpreting the results of this test, it is necessary to rule out the effect of certain drugs (phenothiazine derivatives), and food containing serotonin (bananas, pineapples, nuts, cheese). Increased excretion of 5-hydroxyindolacetic acid is sometimes encountered in coeliac disease.

Carcinoid tumour sometimes produces a melanocyte-stimulating hormone under the effect of which skin hyperpigmentation occurs. In carcinoid tumour of the bronchus, hypersecretion of the adrenocorticotropic hormone with the development of Itsenko-Cushing's syndrome may be encountered. Insulin hypersecretion with the clinical hypoglycaemia syndrome sometimes develops in carcinoid tumour of the pancreas. Affection of the heart in patients with carcinoid tumour sometimes leads to a picture of right-ventricular failure.

Much differential diagnostic significance is also attached to the method of artificial reproduction of typical vasodilatation. A characteristic clinical picture of a flush develops 3 to 5 minutes after taking 25-50 ml of vodka. In appraising the results of this test, it should be borne in mind that repeated intake of alcohol is not attended by characteristic vasodilatation. The duration of the patient's 'areactivity' to repeated intake of alcohol has not been exactly defined. Intravenous infusion of 1-5 μg of adrenalin yields the most constant result.

The indicated extra-intestinal manifestations of the carcinoid syndrome enable it to be distinguished from diarrhoea of other origin. If diarrhoea in carcinoid tumour is not attended by these signs, it may be differentiated from diarrhoea in diffuse reticulosarcoma and from other forms of diarrhoea by the results of biopsy of the small intestine. In the carcinoid syndrome the jejunal mucosa preserves its normal structure. The structural changes in coeliac disease and diffuse haematosarcoma are described in the respective sections. A gluten-free diet is ineffective in the carcinoid syndrome. The characteristic medical history sometimes makes it possible to distinguish coeliac disease from the carcinoid syndrome.

Watery diarrhoea in the carcinoid syndrome is distinguished from that in gastrinoma by a milder course, milder pain syndrome and the absence of a concomitant ulcer in the stomach, duodenum or small intestine. Gastric juice acidity is reduced in the carcinoid syndrome but is always high in gastrinoma. Pancreatic cholera differs from watery diarrhoea developing in the carcinoid syndrome in a larger volume of the daily stool, rapid development of signs of body dehydration and invariable development of the clinical picture of hypokaliaemia.

Crohn's Disease

Crohn's disease is chronic granulomatous inflammation encountered mostly in the small intestine, though it may develop in any part of the gastro-intestinal tract from the oesophagus to the rectum. The inflammation spreads to all the coats of the intestinal wall, to the mesentery, and to the regional lymph nodes. The alternation of affected intestinal areas with healthy ones is a characteristic feature.

At first, Crohn designated the disease terminal ileitis. In accordance with the provisions of the International Congress of Gastroenterologists held in Prague (1968), we describe the differential diagnosis of diarrhoea in segmental enteritis (Crohn's disease, with involvement of the small intestine) and in granulomatous colitis (Crohn's disease with involvement of the colon).

Crohn's disease is characterized by a progressive course with the periodical alternation of exacerbations and remissions. In mild cases the patient may lead a normal life for many years, but in more severe cases he is incapacitated by the development of complications within a few years. In 80-90 per cent of cases the disease begins insidiously and about one and a half to three years pass before the correct diagnosis is made. Crohn's disease with a sudden onset is usually first mistaken for appendicitis or ileus. The true cause of the acute abdomen is only discovered after surgery.

The internist mostly encounters those cases with Crohn's disease which set in unnoticeably. Mild abdominal distension, augmentation of intestinal peristalsis from time to time, the passing of an unusually large amount of gases, and mild diarrhoea are often the earliest signs of the disease. When this short-term diarrhoea occurs after a larger meal than usual, it is mistaken for food poisoning, and when it is encountered in combination with fever, it is erroneously diagnosed as 'the intestinal form of influenza'. In most cases, this mild diarrhoea vanishes within a few days, but sometimes sharp abdominal pain develops in attendance and a picture of ileus or acute appendicitis shapes.

Diarrhoea and abdominal pain are usually the earliest and most constant signs of Crohn's disease. In typical cases they occur simultaneously, but at the onset of the disease they may be encountered independently of one another. According to some authors, diarrhoea precedes the pain syndrome in approximately 20 per cent of cases with regional enteritis and is the first sign in more than half the cases of granulomatous colitis.

Diarrhoea and abdominal pain of more or less long duration cause the patient to lose weight. Without dwelling on the developmental mechanisms of cachexia and focusing attention on the diagnostics,

it may be stated that abdominal pain, diarrhoea and loss of body weight are constant findings in clinically manifest cases of Crohn's disease.

In Crohn's disease, diarrhoea develops gradually as a rule. The frequency and volume of the stool are determined by the localization of the inflammation. If the patient follows a strict diet the stool is passed two or four times a day in regional enteritis and three to ten times a day in granulomatous colitis. The faeces are soft or semiliquid. After a faulty diet they become liquid. In affection of a small segment of the small intestine or colon, watery diarrhoea occurs very rarely. It usually develops under the effect of stress situations or faults in the diet. Watery diarrhoea is encountered more frequently in diffuse jejuno-ileitis than in segmental ileitis.

Signs of deficient absorption of vitamins and electrolytes are very rare in Crohn's disease and are usually found only in diffuse affection of the small intestine and always in combination with steatorrhoea. The stool in such cases has an offending odour. Because of the rich content of fat and gas bubbles, the faeces acquire a greyish clay colour and have a tendency to float on water. In distinction from the stool in ulcerous colitis, the stool in Crohn's disease contains neither blood nor pus. In granulomatous colitis the faeces may contain a small amount of mucus. Tenesmus is not encountered in regional enteritis, but in granulomatous colitis it may occur if the rectum is involved.

In the early stages of the disease diarrhoea may be relieved for a brief period under the effect of the diet. In far advanced cases it becomes permanent. Nocturnal urges to defaecate are often encountered. Diarrhoea is undoubtedly among the principal diagnostic signs of Crohn's disease, but cases are nonetheless encountered in which there are no intestinal disorders. The data of previous authors concerning the incidence of diarrhoea in Crohn's disease are insufficiently convincing because only the total incidence of this sign had been recorded in the past. Authors in the seventies report that diarrhoea is encountered much more frequently in granulomatous colitis than in regional enteritis.

According to summarized statistics of different authors, pain occurs in 67-100 per cent of cases with Crohn's disease. It is often the first and for some time the only manifestation of this disease. In the early stages, the pain is usually felt in the region of the umbilicus, which corresponds with the more frequent localization of the inflammatory process in the distal segment of the ileum.

Pain may be moderate or mild. It appears or intensifies after a meal when peristalsis is augmented. It loses its paroxysmal character with time and becomes continuous. In this later period of the disease, the pain syndrome seems to comprise two components. Paroxysmal pain occurs immediately after a meal, but later becomes

continuous. The development of continuous pain is linked with the spread of the inflammatory process to the mesentery and with the formation of adhesions with the neighbouring organs.

When the inflammatory process is localized in the duodenum, pain is felt in the epigastrium and in the right upper abdominal quadrant. It is often erroneously attributed to cholecystitis. When the inflammatory process develops in the jejunum, pain is felt in the periumbilical region or in the left upper abdominal quadrant. Affection of the most distal parts of the ileum causes pain in the right lower abdominal quadrant where it is often interpreted as pain caused by chronic appendicitis or intestinal tuberculosis. Pain in the sacrum may be associated with spondyloarthritis which is sometimes the early and only sign of Crohn's disease, or with extension of the inflammatory process to the mesocolon.

The formation of adhesions with the neighbouring organs causes their involvement in the inflammatory process, the formation of internal and external fistulae, and perforation of the intestinal wall. Protracted fever and leucocytosis are found in such cases. Perianal and pararectal fistulae and abscesses are encountered particularly often. The true cause of these complications is disclosed only after a long and thorough examination of the patient with close attention paid to his age and the clinical picture of the early stages of the disease.

Women sometimes withstand diarrhoea for long periods without making complaints to a doctor. That is why in each individual case with abdominal pain the patient should be questioned about diarrhoea, the second principal sign of Crohn's disease.

A more or less marked loss in body weight is encountered in 50-75 per cent of cases with Crohn's disease. The underlying factor is anorexia, considerable loss of protein in the faeces, and deficient absorption of nutrients. Inspection of these patients often reveals oedema of the lower limbs first found on the dorsal surface of the feet and later spreading to the subcutaneous tissue of the legs, thighs and small of the back. Ascites developed in some of our patients. In exacerbation of the inflammatory process arthralgia develops, the end phalanges of the fingers and toes thicken and the nails take a convex shape.

In all cases where Crohn's disease is suspected X-ray examination is imperative. It is recommended to begin it with a barium enema which makes it possible to disclose narrowing of the colon, the extent of the narrowing and barium reflux into the terminal segment of the ileum. The ileocaecal reflux is found in approximately half of the healthy individuals. After the barium enema, the small intestine is examined by oral administration of a barium suspension. Because of marked infiltration of the wall and mesentery, the ileum becomes much less mobile on palpation, its lumen

is narrowed, the inner surface becomes uneven, and spinous projections are seen on its outer surface. With the gradual scarring of the ulcers on the inner surface, the lumen is stenosed more and more. The intestinal segment proximal to the stenosis becomes dilated and its diameter grows to 2.5-3.0 cm.

The ileum is involved in 80 per cent of cases with Crohn's disease. Concomitant, usually mild, deformity of the caecum is found in every third patient. Remote stenoses of the small intestine which are usually not extensive are found in about 10 per cent of cases with this disease.

Crohn's disease with involvement of the colon has been intensively studied in recent years. The histological picture of granulomatous colitis is no different in principle from the picture of ileitis. Oedema of the submucosa in this disease terminates in ulceration. Scarring of the ulcers results in stenosis of the intestine. Spread of the process to the serous coat and mesentery is attended by the formation of small abscesses and crypts in them, which are detected because of the spinous projections on the external surface of the intestine.

Simultaneous affection of the terminal ileal segment and one or two segments of the colon is accepted as a characteristic feature. The caecum and ascending colon are involved about as frequently as the rectum and the distal part of the sigmoid colon. Fistulae form in granulomatous colitis just as often as in regional enteritis.

Proctoscopy reveals an inflamed and oedematous mucous membrane on the surface of which occasional ulcers with a mucous or purulent discharge may be seen. The walls of the intestine are rigid and its lumen is constricted in places. Para-anal fissures and fistulae are found in many patients. The discovery of marked inflammatory infiltration of the submucosa and a relatively intact mucosa on biopsy of the rectum is considered to be of high diagnostic value. Granulomas formed of epitheliod cells among which giant cells may be seen are sometimes detected.

The characteristic signs listed are found in only half of the cases with granulomatous colitis.

Aspiration biopsy of the small intestine is often fruitless because the jejunum is very rarely involved in Crohn's disease. Bioptic material may be collected for biopsy from the distal ileum by aspiration or by means of a colonoscope.

The clinical picture of Crohn's disease is very diverse. That is why it is often mistaken for some other disease of the gastro-intestinal tract. It has to be differentiated particularly often from colitis, tuberculous ileotyphlitis and chronic enteritis.

Ulcerative Colitis

Ulcerative colitis (non-specific, non-infectious) is an inflammatory affection of the colon with predominant localization in its left part. Diarrhoea and abdominal pain are the most constant clinical signs of the disease.

Ulcerative colitis prevails among young women and women in their prime. It sets in suddenly or insidiously. Sudden onset is considered a characteristic sign of the disease. In most cases the disease takes a wave-like course, exacerbations alternating with remissions.

Yudin (1968) reported that he had never encountered 'patients suffering from non-specific ulcerative colitis in which the rectum had not been involved'. Most authors of the last decade also claim that the inflammatory process in ulcerative colitis either involves the whole colon at once or it begins in its distal segments and gradually extends in the proximal direction.

Ulcerative colitis incidence in some countries ranges in very wide limits. In recent times it has been showing a tendency to grow everywhere. In most cases the disease begins acutely, simulating dysentery, gastroenteritis, 'food poisoning', and 'intestinal form of influenza'.

Ulcerative colitis may begin as rectal haemorrhage with a formed or loose stool. The admixture of bright red blood in the formed stool makes one immediately think of haemorrhoids. Eventually the stool becomes loose, acquires an offending odour and an admixture of mucus appears in it. During an exacerbation the stool consists of blood and pus and sometimes only of blood. During a remission it acquires a loose consistency or is even formed.

Alternation of diarrhoea with constipation is noted in rare cases. Complaints of constipation are mostly made in inflammation of the rectum and sigmoid colon. Spasm of the proximal healthy intestinal segment prevents entry of the faeces into the rectum. The urge to defaecate is often imperative and a small amount of blood and mucus is discharged. Such urges trouble the patient to an equal degree both during the day and during sleep.

Abdominal pain is not acute in mild cases of the disease. It is commonly localized in the left lower abdominal quadrant but may be felt in the entire abdomen from time to time. Pain of a paroxysmal character is usually accompanied by an urge to defaecate and after evacuation of the intestine it is noticeably relieved. Some patients have pain in the joints, small of the back, and sacrum. Body temperature may be normal or elevated.

Physical examination in severer cases reveals spasm of the sigmoid colon which is palpated as a hard cord. The abdomen is usually soft, the liver is often enlarged.

Mild, moderate, and severe forms of ulcerative colitis are generally distinguished. Mild forms occurring without anaemia, fever, loss of body weight and hypoalbuminaemia are most common. Their onset is usually insidious. Severe forms begin suddenly and are marked by high fever, profuse diarrhoea, intestinal haemorrhage, tenesmus, dehydration, anorexia, hypoalbuminaemia, and oedema of the feet and legs. Moderately severe forms in the degree of their clinical symptoms and signs take an intermediate place.

The fulminating form of ulcerative colitis is particularly severe. It is often complicated by toxic dilatation of the colon (usually its transverse part) and perforation. This last condition may also occur in severe colitis as a complication of a transmural lesion of some area of the colon.

A long-term inflammatory process in the colon often leads to complications which may be divided into local and general. The local, or intestinal complications, are as follows: haemorrhoids, rectal prolapse, the formation of pseudopolyps, anal fissures, perianal and pararectal abscesses and fistulae, rectovaginal and rectovesical fistulae. All these complications develop during an exacerbation of the disease. The gravest local complications are copious intestinal haemorrhage, malignant degeneration, stricture, and the already mentioned perforation and toxic dilatation of the colon.

The general complications of ulcerative colitis include anaemia, hypoproteinaemia, hypokaliaemia, polyarthritis, iritis, trophic ulcers of the legs and feet, amyloidosis, and cachexia.

A tentative diagnosis of ulcerative colitis is made on the basis of the clinical duality consisting of the characteristic diarrhoea described above and abdominal pain. To make a more precise diagnosis it is necessary to resort to X-ray examination of the colon, colonoscopy, and biopsy of the colonic mucosa. The typical clinical course of the disease and the character of the complications developing during it are of high diagnostic value.

Physical examination is usually insufficiently informative in uncomplicated ulcerative colitis, but may prove very valuable for the detection of trophic ulcers of the limbs, disorders of water-electrolyte metabolism, arthritis, peritonitis and some other complications.

The mucous coat of the large intestine is mainly involved in ulcerative colitis. The mucosa of the rectum and sigmoid colon is affected most commonly (in 90-95 per cent of cases). Proctosigmoidoscopy allows these changes to be appraised and often provides invaluable aid in establishing the final diagnosis. The mucosa undergoes characteristic changes in ulcerative colitis. It becomes so dim that the submucosal vessels cannot be seen through it. The surface of the mucosa is no longer shiny or smooth. It becomes uneven, hyperaemic, and granular; the granules are first fine, but

later become coarse. Erosions covered with an exudate are often seen on its surface.

The more acute stage of the disease is marked by a red, drastically oedematous mucosa with a mucopurulent exudate and multiple ulcerations on its surface. Small 'millet-like' greyish-yellow abscesses form under the mucosa. In places the mucosa is covered with a diphtheritic membrane. The mucosa bleeds so easily that the intestinal lumen is continuously filled with sanguinopurulent exudate hindering examination. Pseudopolyps are found frequently; when there are many of them, the mucosa has the appearance of a cobblestone pavement.

Biopsy of the mucosa shows signs of its infiltration with lymphocytes, plasma cells, and eosinophils, degeneration of the epithelial cells, microscopic epithelial erosions, and even cryptic abscesses. Mucosal changes are found in the rectum more frequently than in the sigmoid colon.

X-ray reveals no typical changes in the early stages of ulcerative colitis. With the advance of the disease the relief of the mucosa becomes coarse because its folds are thickened. The outlines of the affected intestinal segments become irregular. In later stages of the disease haustration of the colon disappears, its lumen is constricted and its wall becomes rigid. In a disease of many years' duration, the colon is shortened and its hepatic and splenic flexures are smoothed out and displaced downward. The inner surface of the intestine becomes uneven because of ulcerations, preudopolyps and irregular swelling of some of its areas.

Ulcerative colitis (non-specific, idiopathic) which begins acutely must be, before all else, differentiated from **bacillary dysentery,** in which the pathological process is mostly localized in the colon and, in rare cases, in the distal ileum. Depending on the severity of the infection and the patient's resistance, the affection of the mucosa varies from catarrhal to diphtheritic inflammation. The classical clinical picture of bacillary dysentery is composed of diarrhoea, abdominal pain, and fever. The disease begins abruptly with paroxysmal pain in the abdomen to which diarrhoea soon develops in attendance. In severe cases the stool may be passed up to 24 times a day. It is usually loose and contains much mucus. Blood and pus are found in it in severe cases. Patients often complain of tenesmus and false urges to defaecate which are characteristic of inflammation of the distal rectum. In very severe cases the patient is dehydrated.

Physical examination of a patient at the onset of bacillary dysentery reveals intensified peristalsis, diffuse tenderness of the colon, and a rigid and tender sigmoid colon. The appearance of the colonic mucosa depends on the duration of the disease. At the onset it is always bright red and swollen, but a day or two later punctate bleed-

ing ulcerations appear on its surface, which later coalesce to form large ulcers. The final diagnosis is made after the causative agent is isolated and identified.

Ulcerative colitis differs from bacillary dysentery in the volume and often in the appearance of the stool, the negative results of the search for the causative agent, and the character of course later followed by the disease. The patient's condition with bacillary dysentery may be very grave from the onset. It noticeably improves with time, particularly if antibacterial therapy is applied. The condition of a patient suffering from ulcerative colitis becomes all the more grave with time. Antibacterial therapy is ineffective. Copious intestinal haemorrhage and toxic dilatation of the colon may already develop in the early period of ulcerative colitis. These complications are not encountered in bacterial dysentery.

The importance of arthritis (polyarthritis) in the differential diagnosis of diseases marked by diarrhoea and abdominal pain is mainly determined by the time when it develops in attendance to the principal disease. Arthritis and polyarthritis are encountered in approximately 10 per cent of patients with ulcerative colitis. The clinical picture of polyarthritis precedes the intestinal signs of ulcerative colitis in some cases or develops during this disease in others. Arthritis and polyarthritis never precede bacillary dysentery but are always postdysenteric.

Diarrhoea and abdominal pain are often encountered in **amoebiasis, balantidiasis,** and many other infectious intestinal diseases. Intestinal amoebiasis is the most widespread of them; it is generally subdivided into acute and chronic (recurrent) forms. The causative agent of the disease, *Entamoeba histolytica*, is found everywhere. Infection of the population with it ranges in some countries from 5 to 80 per cent of those examined. A sick person is probably the only source of infection. Asymptomatic carriers of *Entamoeba histolytica* make no complaints, but they may themselves develop the disease at any time or infect others. In the Soviet Union, intestinal amoebiasis is mostly encountered in individuals arriving from countries with a warm climate.

The clinical manifestations of intestinal amoebiasis are mainly determined by the localization of the lesion. The caecum is affected first of all in most cases. The other parts of the colon are involved less frequently and usually later. When *Entamoeba histolytica* is localized in the caecum and ascending colon, the disease sets in insidiously, when it is localized in the sigmoid colon and rectum, the disease begins acutely.

The primary disease follows the course of colitis of the right side, as a rule. Diarrhoea develops gradually. The stool has a sharp odour and is at first loose, later becoming liquid with an admixture of much mucus mixed with faeces or added to them in small clumps.

Paroxysmal pains appear in the adbomen before defaecation; after the stool and gases have passed, the pain is noticeably relieved. In a week or two, diarrhoea and abdominal pain noticeably subside, but mucus is discharged in the stool for a long time. After two or three weeks of apparent improvement, both diarrhoea and the pain syndrome exacerbate. Remissions and exacerbations alternate. The patient's general condition remains compensated for a long time.

An acute onset of the disease with frequent imperative urges to defaecate, a stool containing blood and mucus, and severe paroxysms of abdominal pain are encountered either in primary affection of the sigmoid colon and rectum or in generalization of the infection with the formation of ulcers along the entire colon during an exacerbation. The stool is passed 10 to 12 times a day in such cases, and it sometimes has the characteristic appearance of 'raspberry jelly'. The abdomen is distended and tenderness is elicited on palpation of the colon. The caecum is enlarged and sharply tender to palpation. The sigmoid colon is spastically contracted and tender. The liver is often enlarged.

The clinical picture described above allows a tentative diagnosis of intestinal amoebiasis to be made. The disease has to be distinguished from ulcerative colitis, Crohn's disease, and bacillary dysentery. These diseases often occur with moderate or even high fever. In intestinal amoebiasis body temperature is normal as a rule. The absence of toxicosis and macroscopic admixture of pus in the stool distinguishes acute intestinal amoebiasis from bacillary dysentery and ulcerative colitis.

Proctosigmoidoscopy often yields valuable information for making the differential diagnosis between these diseases. It should, however, be borne in mind that the rectum and sigmoid colon are involved only in some of the cases with intestinal amoebiasis. A normal appearance of the rectal and sigmoid mucosa does not allow the diagnosis of intestinal amoebiasis to be ruled out. Mucosal ulcers with eroded edges are a characteristic proctosigmoidoscopical sign of amoebiasis. They are usually small and flat and are arranged separately from one another. The mucosal areas between these ulcers have a normal pale pink colour.

As it was pointed out above, some ulcers in ulcerative colitis and bacillary dysentery tend to coalesce. Signs of inflammation (swelling, sharp hyperaemia, easy bleeding, the formation of microerosions) are easily found on the mucosa between the ulcers.

The final diagnosis of intestinal amoebiasis is made only after vegatative forms of *Entamoeba histolytica* containing freshly engulfed red cells in the cytoplasm are found. These erythrophages are identified by examining warm faecal matter or matter collected from the floor of an intestinal ulcer. Vegetative forms of *Entamoeba*

histolytica are identified either in a native preparation ('crushed drop') or in preparations stained with iron haematoxylin.

Balantidiasis is a very rare occurrence in the Soviet Union. This is evidently why it is usually mistaken for enterocolitis for a long time. Balantidia parasitize in the wall of the ileum and colon. They cause necrosis of mucosal and submucosal areas with the formation of abscesses and ulcers with irregular borders. Balantidia are found on the floor of these ulcers. Acute forms of balantidiasis are marked by diarrhoea. The stool may be passed four to ten times a day. It is loose or liquid and contains much mucus and in rare cases blood. The disease takes a chronic course with exacerbations and remissions. Paroxysmal pain in the abdomen, diarrhoea, and abdominal distension occur during an exacerbation. Diet therapy has a poor effect. The patients gradually lose weight and anaemia develops.

The clinical manifestations and the results of proctosigmoidoscopy allow balantidiasis to be suspected. The final diagnosis may only be established after isolation of the causative agent. This is done by examining fresh faeces by the native smear method and by treating drops of faeces with Lugol's solution or iron haematoxylin. The faeces usually have to be examined several times and essentially during an exacerbation.

Trial therapy with tetracycline, diodohydroxyquinoline and flagyl distinguishes ulcerative colitis (non-specific and granulomatous) from amoebiasis and balantidiasis. These drugs cause no effect in ulcerative colitis and always produce a remission in amoebiasis and balantidiasis.

Granulomatous colitis is Crohn's disease with isolated affection of the large intestine. It prevails at young age. The proximal part of the large intestine is affected most frequently. In about 80 per cent of cases the terminal part of the ileum is simultaneously involved in the process. Granulomatous colitis resembles ulcerative colitis in its clinical manifestations most closely, but is distinguished from it by the character of the anatomical changes in the intestinal wall, the course of the disease, and the complications.

The morphological basis of the disease is transmural inflammation of the intestinal wall with the formation of deep linear ulcers which constrict the intestinal lumen when they cicatrize. Areas of inflamed mucosa project into the intestinal lumen between the linear ulcers or the scars. The alternation of deep linear ulcers with the areas of inflamed mucosa projecting between them lends the intestinal surface the typical appearance of a 'cobblestone pavement'. Microscopy reveals granulomas in the intestinal submucosal coat. Inflammation of small intestinal areas remote from the principal lesion is regarded as a particularly characteristic feature.

Granulomatous colitis sets in insidiously in most cases and from

its very onset takes the course of a chronic disease with alternating exacerbations and remissions; the exacerbations develop gradually, the remissions appear just as gradually. Diarrhoea, usually with no admixture of blood in the stool, is, in most cases, the first sign of the illness which makes the patient apply to the doctor for advice. Colicky pain in the abdomen is at first felt only after a meal, but later it intensifies and precedes evacuation of the intestine every time.

The general condition of most patients is compensated and they are treated for colitis or enterocolitis for a long time. The disease progresses gradually. Dietary measures prove inadequate in arresting every successive exacerbation. The patient begins losing weight, and anaemia and in some cases signs of the malabsorption syndrome develop. Subfebrile temperature is encountered in about one third of the patients.

In many cases the disease advances so insidiously that the patient usually applies to the doctor for the first time because of its intestinal and extra-intestinal complications: a palpated abdominal tumour formed of fused intestinal loops, perianal fistulae, intestinal haemorrhages which are often erroneously considered to be of haemorrhoidal origin, ileus, arthritis, anaemia and fever of unknown aetiology.

Physical examination in the initial stage of the disease reveals no characteristic signs. In the later stages complications of the disease are mainly discovered; the order of their appearance is often of definite importance in the differential diagnosis. It is most difficult to distinguish granulomatous colitis from ulcerative colitis, because in both diseases there are usually signs of affection of the large intestine. Much less difficulties are encountered in making the differential diagnosis between granulomatous colitis and tuberculous ileotyphlitis, chronic intestinal amoebiasis, metadysenteric enterocolitis, and haematosarcoma of the small intestine which may also be mainly manifested by diarrhoea and abdominal pain.

Both forms of colitis (ulcerative and granulomatous) may cause affection of the large intestine along its entire length or only on some areas. Ulcerative colitis usually begins with affection of the rectum, and lesions of only the rectum are therefore discovered in the early stages of this disease. Isolated affection of the rectum may sometimes occur also in the late stages of this disease.

Granulomatous colitis usually begins in the right half of the large intestine. It may develop in the rectum and sigmoid colon, but the affection is never restricted only to these parts of the intestine. At the same as the rectum and sigmoid colon the transverse or ascending colon may be affected and in 80 per cent of cases the ileum too (Levitan et al., 1974).

Pseudopolyps are discovered in about 10-15 per cent of cases with

ulcerative colitis. They are never encountered in granulomatous colitis. As it is indicated above, simultaneous affection of the ileum is encountered very often in granulomatous colitis and very rarely (at most in 3-5 per cent of cases) in ulcerative colitis. Remote lesions on areas of the large intestine restricted in length occur in about half the cases with granulomatous colitis, but never in ulcerative colitis. Intra-intestinal fistulae very rarely form in ulcerative colitis and are found in about 10 per cent of cases with granulomatous colitis.

According to some authors, granulomatous skin lesions around the anus are a very frequent occurrence in Crohn's disease. Painless fissures and ulcers of the anal canal, deep linear perineal ulcers extending along the scrotum to the base of the penis and to the large pudendal lips, as well as multiple perineal ulcers, are among the signs typical of granulomatous colitis.

Histological examination of tissue taken from the periphery of these ulcers and from the surface of ulcers which sometimes appear in the paraumbilical region, under the mammary gland or in the skin folds on the abdomen discloses characteristic granulomatous lesions of the skin. Granulomatous affection of the squamous epithelium is often found in patients with granulomatous colitis but not in those with ulcerative colitis.

Since the ulcerative and granulomatous forms of colitis affect one and the same organ, they are often manifested by the same signs and their differentiation should therefore be based not on the presence or absence of this or that sign, but on the degree to which it is pronounced, the time of its appearance and the character of its combination with the other signs. Let us clarify this with examples. Diarrhoea and intestinal haemorrhage often develop at the beginning of ulcerative colitis, whereas intestinal haemorrhage is among the late complications of granulomatous colitis. Diarrhoea without intestinal haemorrhage in a patient with a stricture in the proximal parts of the large intestine is extremely characteristic of granulomatous colitis. Such a combination of signs is practically not encountered in ulcerative colitis.

Perianal ulcers are usually solitary and superficial in ulcerative colitis but are often multiple and with characteristically eroded border in granulomatous colitis. The segmental character of the affection, which is typical of granulomatous colitis, is sometimes clearly visible in proctosigmoidoscopy. The rectal mucosa may have a normal pale pink colour and be drastically inflamed only for a distance of 2 to 3 cm.

Ulcerative colitis begins acutely, as a rule, granulomatous colitis, in contrast, sets in insidiously. The stool is passed three to six times daily in granulomatous colitis and may be much more frequent in ulcerative colitis. Exacerbations of ulcerative colitis begin

turbulently, those of granulomatous colitis begin gradually. Tumour of the ileocaecal region and stenosis of the distal ileum are encountered only in granulomatous colitis.

These two diseases also differ in the character of the involvement of the intestinal wall as far as it is possible to judge from the results of biopsy. Ulcerative colitis is marked by affection mainly of the mucous coat, while in granulomatous colitis all the intestinal coats are involved. A particularly characteristic feature of granulomatous colitis is pronounced round-cell infiltration and epithelioid-cell granulomas in the submucosal coat which sometimes contain giant cells; the mucous coat is relatively intact.

Microscopy often reveals changes typical of granulomatous colitis on biopsy of the mucous coat which seems normal on proctoscopy. This inflammation of the submucosa invisible to the eye is a particularly constant occurrence in specimens collected at a distance of 1.0-1.5 cm from the anal sphincter. In ulcerative colitis the inflammatory process is localized in the mucosa and therefore always detected during proctoscopy.

Carcinoma of the Large Intestine

Diarrhoea in combination with abdominal pain and subfebrile temperature is sometimes a manifestation of malignant tumour of the large intestine, which is usually carcinoma. The absence of symptoms specific of this disease often leads to a delay in the diagnosis which may be made 12 to 18 months after the first manifestations had appeared.

The clinical picture is determined by the localization of the carcinoma in the large intestine. The caecum, ascending colon, and the right half of the transverse colon are mainly concerned with the absorption of water, electrolytes and some of the nutrients. The right half of the large intestine is much larger in diameter than the left half. Carcinoma of the right half of the large intestine is rarely complicated by obstruction. It is mainly manifested by disorders of water and electrolyte absorption, impaired nutrition, and fever. The left half of the large intestine serves as a storage for the already formed intestinal contents. Tumour in this part of the intestine is usually manifested by obstruction.

The pain syndrome is among the earliest manifestation of carcinoma. It is encountered particularly often in carcinoma of the right half of the large intestine and in tumous of the small intestine. Persistent pains are one of the early signs of the developing obstruction of the intestine and reflect the inflammatory process in the peritoneum and regional mesenteric and retroperitoneal lymph nodes attendant to the tumour. Body temperature is often elevated

in such cases and rigidity of muscles overlying the tumour appears. A clinical picture develops resembling in many ways the picture of ulcerative colitis, Crohn's disease, and other inflammatory diseases of hollow organs located in the abdominal cavity.

Carcinoma, particularly if found in the left half of the large intestine, often causes intestinal obstruction which in mild cases is manifested by brief episodes of abdominal distension and constipation, and in severer cases by total obstruction. The more distal the localization of the carcinoma, the more frequently it is complicated by intestinal obstruction which usually sets in acutely.

Diarrhoea is among the characteristic manifestations of intestinal obstruction. The stool may be loose or even watery, and may be passed up to ten or twelve times a day. The daily volume of the stool is usually small and rarely amounts to one litre. Diarrhoea characteristically appears after a period of constipation. In carcinoma of the large intestine diarrhoea never lasts long in contrast to diarrhoea in tumours of the small intestine. The periods of diarrhoea in carcinoma of the large intestine always alternate with constipation and with periods in which a normal stool is passed. Diarrhoea is encountered more frequently in carcinoma of the distal parts of the large intestine.

Long-term fever, anaemia, increased erythrocyte sedimentation rate, and sometimes moderate leucocytosis are encountered particularly often in carcinoma of the right parts of the large intestine. Their development is linked with the growth or disintegration of the tumour, with the absorption of the products of its disintegration, and with inflammation of the peritoneum and the regional lymph nodes.

These signs are also often encountered in ulcerative colitis, Crohn's disease, tuberculous ileotyphlitis, intestinal amoebiasis, and other chronic intestinal diseases of the large and small intestine. Blood is always detected in the stool both in carcinoma of the large intestine and in the ulcerative and granulomatous forms of colitis.

Many symptoms and signs of carcinoma of the large intestine are similar to those of the ulcerative and granulomatous forms of colitis, but the differential diagnosis of these diseases does not present much difficulty in most cases. This is mainly explained by the different age of the patients. Most patients suffering from ulcerative and granulomatous forms of colitis are young: the disease sets in before the age of 30 in most of them and before the age of forty in practically all of them. Carcinoma of the large intestine begins after the age of 50 in most cases.

In the granulomatous and ulcerative forms of colitis, anaemia and loss of weight develop after diarrhoea sets in, whereas in carcinoma of the large intestine, they appear long before diarrhoea. In exacerbations of these two forms of colitis, diarrhoea is marked

by its continuous character. It persists for several weeks and even months. Diarrhoea in carcinoma of the large intestine never lasts for a long time.

Diarrhoea predominates in the clinical picture of ulcerative and granulomatous forms of colitis and may be replaced by constipation for a short time. Long-term diarrhoea lasting for months should always be accepted as a convincing argument against carcinoma of the large intestine. Protracted diarrhoea does not rule out an intestinal tumour in general; it only rules out tumour of the large intestine. Diarrhoea and that of a very long duration is an invariable sign of diffuse haematosarcoma of the small intestine.

High differential diagnostic significance should also be attached to the duration of the disease. Patients with carcinoma of the large intestine usually complain of abdominal pain and functional intestinal disorders for months, whereas those suffering from ulcerative or granulomatous colitis may make such complaints for years.

A consistently progressive course is a distinguishing feature of carcinoma of the large intestine, whereas the course of ulcerative and granulomatous forms of colitis is characterized by a wave-like alternation of exacerbations and remissions. During an exacerbation of colitis severe diarrhoea is often replaced by a loose stool which tends to develop into diarrhoea after each more or less serious fault in the diet.

Digital rectal examination, proctosigmoidoscopy and the recently applied colonoscopy with spot biopsy yield very valuable information for differentiating carcinoma of the left half of the large intestine from granulomatous colitis and other inflammatory diseases of the large intestine.

X-ray examination, and especially a contrast enema disclosing the site of the narrowing, are among the most reliable methods for the diagnosis of carcinoma of the large intestine. The results of X-ray examination alone, however, cannot be of decisive importance. Timely recognition of carcinoma of this intestine is possible only from the combination of clinical and X-ray findings.

In making the differential diagnosis between carcinoma of the large intestine with its other diseases, it should be taken into account that carcinoma causes stenosis of the intestine only in one place, as a rule, whereas in the ulcerative and granulomatous forms of colitis, multiple stenoses of the large intestine are often encountered as well as drastic disturbances in its relief for a considerable length.

Tuberculous Ileotyphlitis

Long-term exhausting diarrhoea is sometimes encountered in tuberculous ileotyphlitis which may develop both in the period of primary and in the period of secondary tuberculosis. Besides tuberculous ileotyphlitis, active tuberculous changes are almost always found in the mesenteric lymph nodes and in the genitals. Patients suffering from tuberculous ileotyphlitis have no signs of pulmonary tuberculosis as a rule. The lymph nodes are usually not enlarged. Hard and painless axillary lymph nodes are found occasionally. Small tender nodes are found in the posterior Douglas' space in some females with this disease or the right uterine adnexa are enlarged.

A tendency to constipation is noted from the onset of the disease which is replaced by diarrhoea as a rule. The stool is passed five or six times a day, it is loose with an offending odour and often contains mucus and blood. In simultaneous involvement of the small intestine, diarrhoea may even predominate in the clinical picture. In most cases, however, constipation of three or four days' duration is replaced by a loose stool passed for seven to ten days. In some cases, a small hard lump is first discharged during defaecation followed by soft faeces.

The pain syndrome is usually very marked. The pain is mostly localized in the right ileal or paraumbilical region. It is continuous or paroxysmal. The continuous pain does not depend on the intake of food. Paroxysms of pain are usually associated with severe meteorism. They are relieved or disappear after the stool and gases are passed.

The abdominal wall in the right lower quadrant is tender and often rigid. Diffuse rigidity of the entire abdominal wall is found in rare cases. Hard and more or less thickened walls of the ileum and caecum are felt in the right ileal region in far advanced cases. A tender tuberous tumour is sometimes palpated here.

Body temperature of patients with tuberculous ileotyphlitis is elevated, as a rule, which is clearly associated with physical exertion. Stable subfebrile temperature may last for a long time in some cases, despite the abatement of the local process. The ESR is increased for a long time. Hypersensitivity of these patients to percutaneous and intracutaneous tuberculin injection is a characteristic feature. The Pirquet or Mantoux test often intensifies diarrhoea and pain in the right ileal region and causes elevation of body temperature with progressive general weakness.

X-ray examination discloses a picture which is distinguished with difficulty from Crohn's disease in which the process is localized in the right ileocaecal region. Both diseases lead to thickening of the intestinal wall or to its stenosis. A combination of ulcers and

pseudopolyps is encountered in both diseases, and the mucous membrane may consequently take the appearance of a 'cobblestone pavement' in both. This sign is encountered quite frequently in Crohn's disease but rarely in tuberculous ileotyphlitis.

Involvement of the caecum in the pathological process leads to its deformity which is often disclosed on X-ray. The final diagnosis of the disease is often established only during laparotomy when typical tuberculous ulcers or an eruption of tuberculous nodules are found in the ileocaecal part of the intestine. The diagnosis of tuberculous ileotyphlitis becomes very probable if signs of extra-intestinal tuberculosis or calcification of the mesenteric lymph nodes are found in attendance to the clinical picture described above.

Tuberculous ileotyphlitis has to be differentiated most frequently from tumour of the large intestine, especially from **carcinoma of the caecum.** In his time V. P. Obrastsov pointed out that in carcinoma the caecum is rapidly stenosed, whereas in tuberculous ileitis it remains unobstructed for a long time.

Carcinoma of the caecum is usually palpated only in cachexic patients. Tumour in tuberculous ileotyphlitis may induce diarrhoea and constipation, it often grows to a large size, but the patient's condition may nevertheless still be satisfactory. A high sensitivity to tuberculin is encountered only in tuberculous ileotyphlitis.

In tuberculous ileotyphlitis cicatrization of the ulcers not only causes stenosis of the intestine, but also its shortening. Simultaneous affection of the ileum is characteristic of tuberculosis but is not encountered in carcinoma. When the tuberculous process is localized only in the caecum, the X-ray picture is identical to that of carcinoma of the same localization. It should also be borne in mind that the presence of a tuberculous process in the lungs does not rule out the possibility of carcinoma in the caecum.

Tuberculous ileotyphlitis may resemble intestinal amoebiasis complicated by the formation of amoeboma. Constipation often alternates with diarrhoea in both diseases and cicatrization of the intestinal ulcers leads to stenosis of the intestine. The course of these two diseases and their extra-intestinal signs are so different, however, that the differential diagnosis presents no significant difficulties.

Chronic Enteritis and Colitis

Diarrhoea is the most characteristic sign of enteritis which is usually unattended by abdominal pain. A frequent and loose stool in colitis is often combined with pain. The association of this pain with evacuation of the intestine is regarded as a characteristic feature. It is usually felt before defaecation. The patient's condition improves noticeably after the stool is passed. Diarrhoea with par-

oxysmal abdominal pain is always encountered in disaccharidase deficiency. Other non-infectious diseases may also be marked both by diarrhoea and by pain. Affection of the small intestine prevails in the clinical picture in some cases and affection of the large intestine in others. The difficulties of distinguishing the diseases of this group according to the clinical manifestations led to the unjustifiably wide use of the term enterocolitis. In the Soviet Union it is often used to designate a chronic inflammatory (usually catarrhal) simultaneous affection of the small and large intestine.

The severity of the patient's condition is determined by the character and degree of diarrhoea. The steatorrhoeic stool encountered in milder cases is replaced by watery diarrhoea in gravely ill patients. The more severe the patient's condition the more sharply pronounced is polyfaecalia. The daily amount of faeces during an exacerbation may be 1.5 to 2.0 kg. In watery diarrhoea, the patient may discharge up to three litres of light brown liquid with an offending odour.

Abdominal distension is considered to be the most constant sign of enteritis. The volume of intestinal gases in a healthy person on a mixed diet reaches about 1 litre. The gaseous products are mainly produced during splitting of cellulose by the intestinal bacteria. A healthy person passes about 0.2 litre of gases daily; the remaining amount is absorbed by the blood. In enteritis the production of gases is intensified, while their absorption is impaired. This results in the accumulation of gases in the intestine and distension of the abdomen which usually becomes dome-like. Intestinal peristalsis is augmented and often loud. The feeling of heaviness and distension of the abdomen diminishes temporarily after the gases are passed.

In about half of the cases with chronic enteritis, palpation of the caecum gives rise to a splashing sound. The appearance of this sound is evidence either of active fermentation processes taking place in the caecum, or of entry into it of chyme from the ileum in abnormally large amounts, or of obstruction to the free movement of liquid in the colon.

Long-term and severe diarrhoea is accompanied by disturbed absorption of nutrients, of fat and fat-soluble vitamins in the first place. Hyperkeratosis, night-blindness, osteoporosis and haemorrhages are often encountered in patients suffering from chronic enteritis for a long time. Impaired absorption of iron, vitamin B_{12} and folic acid leads to the development of anaemia which is usually of a mixed character (macrocytic and microcytic). If the patient is kept on a strict diet for a long time and loses abnormally high amount of protein into the lumen of the gastro-intestinal tract, hypoproteinaemia may develop.

Chronic **enterocolitis in pellagra** is an example of chronic enterocolitis of purely alimentary origin.

Diarrhoea always develops in pellagra which is a disease resulting from nicotinic acid and tryptophane deficiency in the diet. It is now recognized that 60 mg of tryptophane are equivalent to 1 mg of nicotinic acid.

The disease begins with a burning sensation in the tongue. Alternating constipation and diarrhoea develop in attendance with time. In severer cases the oral mucosa is bright-red. The mucosa of the stomach, rectum, vagina, and anterior parts of the urethra is also bright-red. The nasal mucosa remains pale. Small ulcerations form on all mucous membranes. The abdomen becomes distended by this time in all patients and watery diarrhoea and characteristic skin lesions develop. Symmetrical spots which are first red and later dirty-brown appear on the face, neck and extensor surfaces of the hands and forearms. The patients become irritable. Paraesthesias of the hands and feet develop later which are sometimes joined by peripheral neuritis. The tendon reflexes disappear and dementia soon develops.

The skin manifestations of pellagra are always clearly pronounced. They are found in places accessible to inspection and are the first to be noticed both by the patient and the doctor. A characteristic medical history combined with the skin signs of pellagra make identification of the cause of diarrhoea in these patients easy. The correctness of the diagnosis is checked by prescribing nicotinic acid. The clinical manifestations of mild pellagra disappear completely 24 hours after parenteral administration of 0.1 g of nicotinic acid.

Long-term colitis is caused in most cases by chronic gastro-intestinal infections. Chronic colitis develops most commonly following acute dysentery. The conversion to the chronic form occurs in some cases almost immediately after the acute stage or after a period of apparent health in others. The absence of bacteriological verification in patients with clinical and morphological signs of protracted post-dysenteric colitis with general phenomena does not rule out dysentery and calls for thorough differential diagnostic work. The final diagnosis may be established only after a more or less lengthy follow-up of the course of the disease.

Chronic enterocolitis is characterized by the prevalence in the clinical picture of signs of involvement of the small intestine (deficient xylose absorption, steatorrhoea, X-ray signs of enteritis, and normal appearance of the rectal and sigmoid mucosa). The combination of diarrhoea with disorders of vitamin absorption, polyfaecalia and the appearance of watery diarrhoea during exacerbations are also characteristic features.

Polyfaecalia, impaired vitamin absorption, steatorrhoea and watery diarrhoea are never encountered in exacerbations of dysenteric colitis. The mucosa of the rectum and sigmoid colon in dysen-

teric lesions is changed and various signs of inflammation are usually seen on its surface during proctoscopy.

In appraising the differential diagnostic significance of some tests it should be borne in mind that disorders of vitamin B_{12} absorption make the association of diarrhoea with dysentery doubtful, while impaired absorption of folic acid or xylose makes this association practically improbable. Vitamin B_{12} is absorbed in the lower part of the ileum which in rare cases may also be involved in dysentery. Folic acid is absorbed in the jejunum whose dysenteric affection is hardly probable. Xylose is absorbed along the entire length of the small intestine, but the results of its absorption over the first two hours are only determined by the functional condition of the jejunum. The findings of aspiration biopsy of the jejunum which is involved in enteritis but not in dysentery may be of great assistance in the differential diagnosis.

The clinical picture of chronic enterocolitis with diarrhoea and abdominal pain often develops in **lambliasis** the causative agent of which *(Giardia intestinalis)* inhabits the duodenum, the proximal part of the jejunum, and the bile ducts. Cysts form in the distal parts of the small intestine. They are usually found in the faeces, but in severe diarrhoea the stool may also contain vegetative forms.

There is usually no tenesmus in diarrhoea in lambliasis. The stool is usually loose, rarely liquid. It is passed four or five times a day. Mucus is always contained in it, an admixture of blood only in cases of very massive infestation. The abdomen is usually distended and there is diffuse tenderness on palpation. When the disease is of a long duration, signs of the malabsorption syndrome (hyperkeratosis, anaemia) may appear.

The diagnosis is made after vegetative forms of *Giardia intestinalis* are detected in the duodenal contents or faeces.

The causative agent of **intestinal trichomoniasis** is a parasite of the large intestine. It may cause catarrhal colitis independently but more frequently it sustains a pathological process induced by other causative agents. The infestation is manifested clinically as diarrhoea often with imperative urges to defaecate. The stool is loose with no odour and is passed two or three times daily at most. Signs of colitis are found on proctosigmoidoscopy. The diagnosis is established when parasites are identified in native smears prepared from freshly discharged faeces diluted with physiological saline solution.

Diarrhoea with abdominal pain is sometimes encountered in **helminth infestations**, namely in enterobiasis, trichocephaliasis, strongyloidosis, ascariasis and hymenolepiasis, the causative agents of which parasitize in the small intestine. The generally accepted opinion that the clinical signs of diarrhoea disappear soon after anthelminthic treatment is completed is far from always confirmed. Observation over US infantrymen in Vietman showed that diarrhoea may

persist for four to eight months after the invasion is eliminated. The persistence of diarrhoea and the malabsorption syndrome in these cases was attributed to chronic jejunitis, the signs of which were discovered during aspiration biopsy of the small intestine.

It is probably most difficult to distinguish chronic enteritis from **coeliac disease,** in which meteorism, diarrhoea and signs of the malabsorption syndrome are also encountered. The small intestine is involved in both diseases. The main distinguishing feature between them consists in the different extent of its involvement. Habit and experience allow these differences to be detected at the patient's bedside.

It is essential before all else to gain information about the beginning of the disease. In most cases coeliac disease sets in in childhood. Its clinical manifestations disappear completely in puberty but recur in the prime of life. Chronic enteritis develops in most cases after some acute gastro-intestinal disease or after a lengthy period of an inadequate diet. The disease begins at young or middle age.

Ordinary diet therapy always produces a remission in chronic enteritis but is always ineffective in coeliac disease. A gluten-free diet is highly effective almost in all cases of coeliac disease. A remission occurs one or two weeks after it is prescribed.

The malabsorption syndrome is encountered both in chronic enteritis and in coeliac disease, but is far more manifest in the latter disease. On inspection of patients suffering from coeliac disease, the skin is found to be atrophied and its surface dry and scaly.

Disorders of electrolyte metabolism are sharply manifest in coeliaca. Patients often complain of considerable muscle weakness, especially in the proximal muscles of the limbs. They find it difficult to raise their arms. Osteoporosis may be so severe that spontaneous bone fractures sometimes occur and X-ray signs of osteoporosis are always found. Iron and folic acid deficiency anaemias are among the constant signs of coeliac disease.

The signs listed above are also often encountered in chronic enteritis, but are less manifest than in coeliac disease and develop only after many years of the disease. Hypoproteinaemia is observed also in cases of severe chronic enteritis but in coeliac disease it is manifested so sharply that leads to the development of hypoproteinaemic oedema.

The differential diagnosis of these two diseases is made much easier if biopsy of the small intestine is performed. In coeliac disease the histological preparations show characteristically changed structure of the mucosal coat of the small intestine. In chronic enteritis, in contrast, only increased infiltration of the submucosal coat and more or less marked increase in the number of cells at the base of the crypts are found.

Chronic enteritis has to be distinguished in rare cases from lym-

phosarcoma which, as our experience shows, is sometimes also mistaken for coeliac disease. Absorption may already be impaired in the first stage of the development of the tumour (in infiltration of the wall of the small intestine or the mesenteric lymph nodes with mature lymphocytes or plasma cells) but mostly it is disturbed in the stage of the transformation of this benign process to a malignant process (lymphosarcoma).

In our patients lymphosarcoma of the small intestine set in either insidiously with no obvious cause or after influenza or food poisoning. The first manifestations of the disease were abdominal distension and diarrhoea which took an intermittent course. Brief periods of its exacerbation were replaced by brief remissions. The stool was neither frequent nor copious. There was no noticeable loss in weight and the patient's general condition was satisfactory.

Oedema appeared for no apparent cause between the 5th and 9th months of the disease. The nails became convex and the distal phalanges of the fingers took the appearance of drumsticks. At this period of the disease marked hypoproteinaemia was found in all patients and achlorhydria in 75 per cent of patients. Thus, in the early period of the disease diffuse lymphosarcoma of the small intestine is manifested by the disturbances mainly of the metabolism of blood plasma proteins.

The full clinical picture of diffuse lymphosarcoma of the small intestine occurred acutely and also with no obvious cause. Diarrhoea immediately changed from intermittent to permanent. The stool became copious, fatty, often foamy and watery. The patients lost weight rapidly, 15 to 20 kg in six to twelve months. A picture of a severe malabsorption syndrome developed in addition to marked cachexia. There was no enlargement of the subcutaneous lymph nodes or spleen.

The X-ray signs of the disease appear only in the late stages. They consist in thickening of the duodenal and jejunal mucosal coats. Pathognomonic signs are rounded filling defects and crescent shaped depressions on the outlines usually of the duodenum and ileum, polyp-like protrusions into the intestinal lumen, alternation of dilated and stenosed areas, and rigidity of the walls at the sites of the stenoses.

The clinical picture of diffuse involvement of the small intestine in lymphogranulomatosis resembles that of lymphosarcoma in all respects but differs from it only by the presence of the pain syndrome. Abdominal pain in primary lymphogranulomatosis of the small intestine has the character of paroxysms. Intensification of diarrhoea in lymphogranulomatosis is attended moreover by marked disorders of water-electrolyte metabolism (muscle weakness, tetany). Fever was not a constant occurrence in cases of lymphosarcoma but was often found in patients with lymphogranulomatosis.

In most cases diffuse haematosarcoma was localized in the proximal jejunal segment where folic acid and xylose are absorbed. Vitamin B_{12} absorption in this localization of the tumour is normal. It is impaired when the tumour is localized in the ileum, in which case the absorption of xylose and folic acid is normal. In chronic enteritis the absorption of xylose and vitamin B_{12} is often simultaneously impaired. The findings of aspiration biopsy of the small intestine make the differential diagnosis of diarrhoea much easier, but it is precisely in haematosarcoma that this method often fails because of the focal character of the intestinal lesion.

The diagnosis of diffuse haematosarcoma of the small intestine should be considered in every patient with a clinical picture of chronic enteritis because its early recognition and the current method of therapy make it possible to restore the working capacity of the patient for several years and to preserve his life for many years. It should be emphasized, however, that early diagnosis of diffuse haematosarcoma is an extremely difficult task.

Crohn's disease both in the form of regional enteritis and in the form of granulomatous colitis often begins with diarrhoea which is at first mistaken for chronic enterocolitis. The differential diagnosis between Crohn's disease and chronic enteritis may be made at the patient's bedside in most cases.

In Crohn's disease diarrhoea is often combined with elevated body temperature. Even in severe cases of chronic enteritis, body temperature is normal. Attention should also be paid to the difference in the pain syndrome. A patient with chronic enteritis complains of a sensation of abdominal distension; there are no sharp or severe pains.

In cases with Crohn's disease there are almost always complaints of mild distension in the right lower abdominal quadrant which is replaced by pain when the chyme passes through the ileocaecal valve.

The origin of this pain is evidently associated with stimulation of the muscular and serous coats of this narrowed ileum and its mesentery. These structures in a patient with chronic enteritis are not involved in the inflammatory process and the passage of chyme along the ileum therefore remains unnoticed. A tender dense swelling is often palpated in the right ileal region in Crohn's disease. Such a swelling is never palpated in patients with chronic enteritis.

The results of inspection of the perineum and rectal mucosa are likewise of high differential diagnostic importance.

In Crohn's disease the perineal skin is often changed because of specific inflammation, Pararectal fistulae and painless ulcers with eroded edges are found here in far-advanced cases. Such changes are not typical of chronic enteritis.

The rectal mucosa may appear normal in both diseases, but in

Crohn's disease biopsy of this seemingly normal mucosa often reveals signs of inflammation of the submucosal coat and deeper coats of the intestinal wall. Such changes are not encountered in chronic enteritis. Xylose absorption is normal in Crohn's disease but is usually disturbed in chronic enteritis. It is particularly sharply impaired during the first two hours of the tests.

X-ray examination reveals stenosis of the terminal part of the small intestine and stenosis of segments of the jejunum and large intestine. In chronic enteritis the intestine is not stenosed.

Tuberculous affection of the intestine is now very rare and is quite easily distinguished from chronic enteritis. Considerable differential diagnostic difficulties arise only in primary infection with tuberculosis through the gastro-intestinal tract. Tuberculous bacilli penetrate the intestinal mucosa in such cases and enter the mesenteric lymph nodes in which a specific inflammatory reaction develops with the formation of caseuos necrosis. Ulcerative forms of affection of the small intestine are very rare in primary tuberculosis. They do not differ from secondary ulcerous tuberculous enteritis in the clinical manifestations. The differential diagnosis between chronic enteritis and tuberculous affection of the intestine is based on the difference mainly in the clinical manifestations of diarrhoea and the pain syndrome. Tuberculous affection of the large intestine is very rare.

There are no severe pain sensations in common chronic enteritis. The patients may have a sensation of abdominal distension, but not pain. In tuberculous intestinal infection the pain syndrome is always manifested very clearly because the mesentery is involved in the inflammatory process. Abdominal pain is the main and most frequent complaint of these patients. The pain occurs after a meal, is of a colicky character and is usually so sharp that sitophobia may develop. In most cases the pain is localized in the right lower abdominal quadrant, less frequently it is felt in the periumbilical region and the hypogastrium. Diffuse abdominal pain is encountered in rare instances.

Diarrhoea in chronic enteritis sharply differs from that in tuberculous affection of the intestine. Chronic enteritis is marked by alternation of remissions and exacerbations. Periods of pronounced and sometimes severe diarrhoea are replaced by periods of relative well-being. Diarrhoea in tuberculosis of the intestine (like that in Crohn's disease) is distinguished by a torpid course. Once it afflicts a patient it becomes permanent. A soft or loose stool passed 3 to 6 times daily often contains a large amount of fat and fatty acids. Depending on the severity of the steatorrhoea, its odour varies from the usual to sharply rancid.

Marked loss of body weight is often encountered in **tuberculous**

enteritis mostly because of sitophobia and anorexia. In approximately half of the cases a tender cord, the terminal segment of the ileum, is palpated in the right ileal region. Persistent fever is found in approximately one third of patients with intestinal tuberculosis.

The X-ray findings make the differential diagnosis between chronic enteritis and tuberculosis of the small intestine much simpler. The involved intestinal segment (usually the ileocaecal region) hardly contains any barium while the adjacent proximal and distal segments are filled with large amounts of it.

It should be remembered that this sign is not encountered in every case of intestinal tuberculosis. The barium may be seen as a thin stream in the lumen of the small intestine, which is evidence of its stenosis or extreme intensification of its motor activity under the effect of inflammation.

Carbohydrate Intolerance

Approximately 9 per cent of all patients in gastro-enterological departments suffer from carbohydrate intolerance (Bockus, 1976). The current study of these fields of pathology has been conducted for a relatively short time. In 1959 Holzel et al. described a clinical syndrome arising as a consequence of disturbed disaccharide digestion. In 1962 Lindquist et al. and Laplane et al. reported on chronic diarrhoea caused by monosaccharide malabsorption. The combined discoveries of these researchers gave rise to the modern theory of disaccharidase deficiency, a clinical condition induced by disorders of disaccharide digestion and absorption.

Disaccharides are broken down into monosaccharides on the membrane of the epithelial cells of the small intestine under the effect of the enzymes maltase, sucrase and lactase. Reduced disaccharidase activity may be congenital or acquired. Acquired disaccharidase activity developing in an adult under the effect of diseases of the small intestine suffered in the past usually has to be dealt with in the clinic of internal diseases.

Deficient activity of lactase concerned with the hydrolysis of milk sugar to glucose and galactose is most frequently encountered. Maltose is hydrolised by four enzymes and deficient breaking down of this disaccharide is therefore a rare abnormality. Deficient lactase activity is sometimes encountered in adults as an isolated disease, but most frequently it complicates other gastro-intestinal diseases. It is practically always found in patients who had been operated on for resection of the stomach and in patients with ulcerative colitis and the large intestine stimulation syndrome.

Disaccharidase deficiency is quite common in diseases of the small intestine: coeliac disease, tropical sprue, gastroenteritis, giardiasis,

kwashiorkor and other diseases caused by malnutrition. Resection of a large segment of the small intestine is also marked by disaccharidase deficiency because of the mechanical reduction of the number of enzymes contributing to disaccharide digestion.

Irrespective of the cause of its origin disaccharidase deficiency is always attended by disorders of parietal carbohydrate digestion in the small intestine. As a result the disaccharides that were not broken down enter the caecum where they are hydrolysed under the effect of lactic acid fermentation bacteria, enterococci and some clostridial bacteria, *Clostridia welchii* in particular, with the formation of lactic, acetic and other organic acids, carbon dioxide and hydrogen. Two to four molecules of organic acids form from each disaccharide molecule during this process. This is attended by elevation of osmotic pressure in the caecum and the ascending colon.

Water and electrolytes are absorbed in the right parts of the large intestine of a healthy person. In a patient with disaccharidase deficiency the function of this part of the intestine is distorted. Because of the high osmotic pressure, the fluid entering this part of the intestine is retained in its lumen. As a consequence, the volume of the faeces increases and they are liquefied. In patients with disaccharidase deficiency the bulk of the daily stool is two- to tenfold that of a healthy person. In severe cases of disaccharidase deficiency dehydration of the patient is combined with increased electrolyte loss.

It is assumed that lactic, acetic, propionic, butyric and other organic acids accumulating in the lumen of the large intestine produce a stimulating effect on it. Despite its attractive simplicity and popularity, probably stemming from this, the assumption from the standpoint of a clinician does not seem convincing. The recta and sigmoid mucosa in patients with disaccharidase deficiency is pale pink and no signs of its inflammation are found.

Pronounced bacterial fermentation in the lumen of the large intestine is marked by the production of a large amount of gases which in turn leads to distension of the intestine. Its peristalsis is augmented and can often be heard at a distance. The passing of gases increases noticeably and always relieves the sensation of stomach discomfort. All the abovestated clarifies the origin of the main clinical signs of disaccharidase deficiency (diarrhoea, abdominal pain, and abdominal distension attended by increased passing of gases).

Lactose intolerance is the most common form of disaccharidase deficiency encountered by an internist. It may be congenital or acquired. The incidence of the congenital form is particularly high among the black population. According to the different authors this or that degree of lactose intolerance is found in 40 to 100 per cent of the black people who were examined. Reduced lactose ac

tivity is revealed in approximately 75 per cent of Jews and 63 per cent of Canadian Indians. Lactose intolerance is encountered in 2-19 per cent of the European population.

The clinical picture of disaccharidase deficiency has been studied most thoroughly in patients with reduced lactose activity. The clinical manifestations of the disease are very diverse. The presence of this or that sign of the disease and its severity are determined by the amount of lactose taken and the rate of its entry into the small intestine. In some cases the patient may have no complaints and no unpleasant sensations, while in others he may have colicky abdominal pain. Periods of constipation may be replaced by attacks of severe diarrhoea. Signs of the malabsorption syndrome, usually moderate, develop in cases of severe diarrhoea.

Abdominal pain is encountered in almost all patients. Its intensity ranges from an indeterminate sensation of pressure in the abdomen to severe paroxysms of pain suggesting ileus. The pain is noticeably intensified after a meal and before defaecation. Intensification of pain at night ('alarm-clock diarrhoea') is particularly characteristic. The patient feels greatly relieved after defaecation or when a large volume of gases has been passed.

Almost all patients complain of abdominal distension and loud borborigmus which usually terminates in the passage of odourless gases. The sensation of abdominal distension is relieved after eructation which is almost constantly encountered in such patients.

The stool may be soft, loose, foamy and, in severer cases, watery. It has a characteristic sharply acid reaction and a sour odour and sometimes the odour of vinegar. The patients are usually well aware that diarrhoea, the pain syndrome, and the dyspeptic phenomena are associated with drinking milk. They either refuse to drink it, or take it as a purgative. If the connection between drinking milk and the appearance of gastro-intestinal disorders is not recognized, the disease is often mistaken for colitis or enterocolitis, for which the patient is often treated for a long time and with no success.

Diminished lactase activity in the epithelium of the small intestine is recognized by means of three methods: tests for milk sugar tolerance, tests for intestinal lactase activity and the prescription of a test diet free of milk sugar. Since these diagnostic methods have as yet not become widely applied, they are briefly described below.

The patient takes no less than 50 g of milk sugar (1 g/kg) dissolved in 0.5 litre of water on an empty stomach in the morning. Blood samples for testing the glucose concentration are taken by the same method as in tests for sugar tolerance. The blood glucose concentration in a healthy person increases by more than 20 mg/100 ml during this test. If the increase in the concentration is less, deficient activity of the intestinal lactase may be presumed.

A patient with reduced intestinal lactase activity has abdominal pain, distension of the abdomen with passage of a great volume of gases and diarrhoea in one to six hours after taking this dose of milk sugar. Lactic and acetic acids are found in the faeces but the stool pH in adults may be normal. The appearance of these symptoms after the milk sugar tolerance test is evidence of deficient disaccharidase activity but their absence does not rule out this diagnosis. When lactase activity is reduced only mildly the clinical manifestations may be very mild or absent altogether.

A direct test for lactase activity is conducted on biopsic material of the small intestine. Two biopsic specimens are generally collected; one for histological examination and the other for testing enzyme activity. The latter is rapidly frozen in liquid nitrogen or dry ice and disaccharidase activity expressed in units per 1 g of protein or per 1 g of dry mucosal mass is determined in its homogenates. Disaccharidase activity does not change with age and in a healthy person ranges from 4 to 149 units/1 g protein.

In practical diagnostic work there is no need to test disaccharidase activity in every individual suspected of having this disease. If the clinical signs of intolerance develop in a patient after he takes 50 g of milk sugar (or its equivalent, i.e. 1 litre of milk) it is obvious that he is suffering from reduced disaccharidase activity. If the need arises to confirm the diagnosis the test for milk sugar tolerance is performed in which 50 g of milk sugar is given per os or 30 g is poured through a duodenal catheter directly into the jejunum. The second variant of the test excludes the dependence of its result on disorders of the stomach reservoir function. It is recommended for patients who had undergone resection of the stomach.

To be convinced that the blood glucose 'flat curve' depends exclusively upon reduced lactase activity, a tolerance test for monosaccharides, components of lactose (i.e. 25 g of glucose and 25 g of galactose), is performed. After this test patients with deficient lactase activity do not develop signs of milk sugar intolerance while the blood glucose content proves to be above the initial level by more than 20 mg/100 ml. Simultaneous tests for the content of glucose and galactose in the blood make it possible to judge the capacity of the patient to absorb these monosaccharides.

Monosaccharide malabsorption was discovered in 1962. The clinical picture consequent upon deficient absorption of glucose and galactose has been described to date. This disease is evidently encountered more frequently than it is diagnosed. Light microscopy shows normal mucosa of the small intestine in these patients. The disease is manifested by watery diarrhoea occurring both after taking disaccharides and after the prescription of monosaccharides. Fructose absorption in these patients is normal. The symptoms of

the disease disappear when a diet in which fructose is the only source of carbohydrates is prescribed.

Reduced activity of intestinal maltases is a much less frequent occurrence than lactase deficiency. It is manifested clinically by intolerance to sugar, starch and the products of its breakdown. The stool may be soft or watery with a characteristic vinegar odour. Diarrhoea, abdominal distension and pain disappear after sugar and starch are removed from the diet. The disease is mostly encountered among children. Its clinical manifestations noticeably diminish with age.

Persons with mushroom intolerance are encountered at times. The disaccharide trihalose contained in mushrooms is broken down in the wall of the small intestine into glucose under the effect of the enzyme trigalase. In reduced activity of this enzyme, mushrooms, particularly early ones, containing a large amount of trihalose cause sharp abdominal distension, watery diarrhoea and colicky pains in the abdomen in persons with reduced activity of this enzyme. The clinical signs appear immediately after the meal and persist for several hours. The clinical picture of the disease is easily reproduced after taking the pure disaccharide or eating early mushrooms.

As it is noted above isolated milk sugar intolerance is a disease widely spread both among children and adults. Isolated deficiency of other disaccharidases is very rare. It is usually found simultaneously with reduced lactase activity. The internist has to deal with disaccharidase deficiency in patients who had undergone resection of the stomach, resection of a large segment of the small intestine and particularly frequently in gastroenteritis, food poisoning, giardiasis, strongyloidosis, bacillary and amoebic dysentery, Crohn's disease and in ulcerative colitis.

Disaccharidase deficiency is sometimes found in patients who have no signs of any organic disease of the gastro-intestinal tract. This is why it may be accepted as a rule to perform the test for milk sugar tolerance in all patients with diarrhoea and abdominal pain of unrecognized origin. It should also be remembered that disaccharidase deficiency often complicates the course of the other gastro-intestinal diseases and that its timely detection may noticeably improve the efficacy of their management.

Functional Diarrhoea

Every internist often has to treat patients suffering from recurrent diarrhoea and in whom the most scrupulous examination and long years of surveillance fail to disclose any organic disease of the gastro-intestinal tract. This functional diarrhoea (nervous, cortico-vesceral) usually occurs in severe emotional stress (e.g. during

university examinations, when presenting a thesis, in taking a new job, in making major decisions on marriage and divorce).

In mild cases, the stool is soft or loose and is usually passed no more than three to five times a day. In severe cases it becomes liquid and is passed up to six to eight times a day. The volume of the stool is in inverse proportion to its frequency. In a very frequent stool tenesmus appears which is usually moderate. Neither fat nor blood nor pus is found on examination of the faeces. An admixture of mucus is detected quite frequently; in some cases it is evenly mixed with the faeces, in others it is found on their surface.

The abdomen is often distended and the abdominal wall moderately tender. Tenderness is sometimes elicited on palpation of the sigmoid colon. Sharp paroxysmal abdominal pains are encountered in functional diarrhoea marked by the excretion of mucus.

The urge to defaecate, which is often imperative, appears immediately after a meal, which allows it to be linked with increased activity of the mechanisms of the gastro-intestinal reflex. Detailed questioning of the patient often convinces one of the justness of the assumption. The urges to defaecate occur in the morning, immediately after breakfast, and during the day after each meal. At night the patient sleeps untroubled. Each patient must be carefully questioned in regard to this important differential diagnostic sign without prompting him to make this or that answer. Sometimes the urge to defaecate occurs only before a meal, sometimes also before and after a meal.

Diarrhoea may persist for several days or weeks. Though the stool in functional diarrhoea is often passed more frequently than in organic gastro-intestinal diseases, the patient's general condition is quite satisfactory and neither cachexia nor signs of the syndrome of nutrient and vitamin malabsorption develop.

It is relatively easy to make a tentative diagnosis of functional diarrhoea (nervous, cortico-visceral in origin) if its occurrence may be linked in time with periods of emotional stress and if steatorrhoea and signs of inflammation are not detected on inspection and laboratory examination of the stool. The final diagnosis may only be established when diseases marked by diarrhoea or capable of being complicated by diarrhoea are ruled out.

In cases with an unknown or insufficiently convincing medical history, functional diarrhoea with an acute onset must be distinguished from bacillary and amoebic dysentery, ulcerative colitis, Crohn's disease and carcinoma of the large intestine. Functional diarrhoea with a less acute course may be mistaken initially for disaccharidase deficiency or for diarrhoea complicating the course of some endocrine diseases.

Simple examination of the faeces yields very important information for differentiating functional diarrhoea from bacillary dysen-

tery and protozoal and ulcerative colitis. Blood and pus are often contained in the stool in these diseases but are never found in functional diarrhoea. Patients with these diseases have an urge to defaecate both during the day and at night. In functional diarrhoea the patient's sleep is usually untroubled at night. Fever, leucocytosis, increased ESR and signs of more or less marked toxicosis are often encountered in the diseases listed above, but not in functional diarrhoea.

Digital rectal examination and proctosigmoidoscopy must be performed in every case of functional diarrhoea. No signs of inflammation of the mucous membrane of the large intestine are found. X-ray examination of the large intestine in functional diarrhoea shows a normal relief of the mucosa and often signs of spastic contraction of the transverse colon but no organic changes are detected in the large intestine.

Diarrhoea in disaccharidase deficiency is probably often mistaken for pure functional diarrhoea. It is also characterized by recurrences and no organic changes are found in the large intestine either. Abdominal distension, pain and borborigmus, and a splashing sound in the caecum are constant findings in all cases of disaccharidase deficiency. Abdominal distension is not typical of functional diarrhoea, the production of gases is much weaker than in disaccharidase deficiency the exclusion of which is an indispensable condition in establishing the diagnosis of functional diarrhoea.

Recurrent diarrhoea often develops in patients who had undergone resection of the stomach or small intestine, in patients with intestinal anastomoses, in cirrhosis of the liver, in thyrotoxicosis, in diabetes mellitus and in other endocrine diseases. Diarrhoea does not predominate in the clinical picture of these diseases but is always only one of the signs of the principal illness. No difficulties are usually encountered in differentiating it from functional diarrhoea. A normal content of fat in the daily stool is convincing testimony against the connection of diarrhoea with a disease of the pancreas, liver, or biliary tract.

The term **mucous colic** designates a clinical condition characterized by the excretion of large amounts of mucus of a non-inflammatory origin from the rectum and increased motor activity of the intestine. At one time this affliction was called mucous colitis or mucomembranous colitis. Lorie (1957) claimed that it could be designated 'intestinal asthma' by analogy to bronchial asthma. The true cause of the syndrome is unknown.

Mucous colic just as functional (cortico-visceral) diarrhoea is mainly encountered in young and middle-aged individuals. Its incidence among females is fivefold that among males. Bockus (1967) points out that mucous colic is not encountered among children and old people of either sex. It is our experience that this dis-

ease, once begun at a young age, may persist in old age. Proctosigmoidoscopy and postmortem examination show no signs of inflammation in the wall of the large intestine. Attacks of mucous colic usually occur during severe emotional stress.

Mucous colic usually begins with severe, often unbearable pain the duration of which may differ even in one and the same patient. Maximum pain is felt in the left lower abdominal quadrant. It is referred to the coccyx and upper part of the thighs. It may occur in attacks or be continuous. In the last case the pain is relieved for different lengths of time a few hours after it sets in.

A large amount of mucus mixed with the faeces or mucus alone with an offending odour is excreted from the rectum during the attack of pain. Sometimes the mucus has the appearance of films. Diarrhoea usually lasts several days. The stool may be passed 10 to 20 times a day. During the colic the mucous membranes of the rectum and sigmoid colon may be hyperaemic or pale. A large amount of mucus is also found on the wall and in the lumen of the intestine.

X-ray reveals spasm of the large intestine which is most marked in its left parts. The spasm of the sigmoid and descending colon is sometimes manifest so sharply that they are seen on the radiograph as a curved thread (the string sign). Marked emotional instability is encountered in patients not only during the mucous colic, but also in periods clear of the attacks of pain.

Supplement VIII-1

Causes of Diarrhoea

1. Tumours of the gastro-intestinal tract.
   Gastrinoma.
   Pancreatic cholera.
   Carcinoid tumour.
2. Crohn's disease.
3. Ulcerative colitis.
4. Bacillary dysentery.
5. Intestinal amoebiasis.
6. Balantidiasis.
7. Granulomatous colitis.
8. Carcinoma of the large intestine.
9. Tuberculous ileotyphlitis.
10. Chronic enterocolitis.
    Pellagra.
    Chronic infections and invasions of the gastro-intestinal tract (dysentery, giardiasis, trichomoniasis, invasion by helminths).
11. Coeliac disease.
12. Lymphogranulomatosis and lymphosarcoma.
13. Tuberculous mesadenitis.
14. Lactose intolerance.
15. Monosaccharide intolerance.
16. Reduced activity of intestinal maltases.
17. Trigalose intolerance.
18. Functional diarrhoea.
19. Mucous colic.

Chapter IX

Enlargement of the Lymph Nodes

Diseases of the lymph nodes are manifested by disorders of the structure and function of one or simultaneously of several organs. In the early stages of different diseases, some one group of nodes is affected, but in later stages simultaneous involvement of several groups of lymph nodes, usually the cervical, axillary and inguinal, occurs. The popliteal and cubital nodes are involved in the process much less frequently. Enlargement of the mediastinal nodes can only be detected by X-ray. Retroperitoneal nodes are best demonstrated by means of isotope scanning.

Enlargement of only one group of lymph nodes is designated as a local affection; the simultaneous enlargement of several groups of lymph nodes is regarded as a generalized affection. Such a division is often conditional, because one and the same disease may be marked both by local and by generalized involvement of the lymph nodes. Marked splenomegaly and hepatomegaly are often encountered in most of these diseases.

Generalized enlargement of the lymph nodes usually occurs in tumours, diffuse diseases of the connective tissue, systemic infections, and some other diseases listed in Supplement IX-1.

Tumours Arising from the Lymph Nodes

Lymphogranulomatosis. The clinical manifestations of lymphogranulomatosis are diverse. This is explained by the possible involvement in the morbid process of lymph nodes of any organ. In most cases (approximately 85 per cent) the disease begins with enlargement of one or more lymph nodes on the neck and only in 6 to 20 per cent of patients the axillary nodes are affected earliest. Affection of the mediastinal and inguinal nodes is third in frequency. Affection of lymph nodes of other regions is much less frequent. The beginning of a disease with involvement of lymphoid tissue which is not a component of the lymph nodes is an extremely rare occurrence.

Fever develops in every case of lymphogranulomatosis. In some cases it is the initial, and for some time, the only sign of the disease. Affection of the superficial lymph nodes, however, may not be attended by elevation of body temperature. The development of ir-

regular-type fever indicates that the lymphoid tissue of the internal organs is involved in the process. Wave-like fever attended by profuse sweating at night is considered characteristic of affection of the mediastinal and abdominal organs. Remittent fever with severe chills is encountered either in lymphogranulomatosis following an extremely severe course or in its combination with bacterial, virus, fungus, tuberculous or some other infection.

Pain is the third, principal diagnostic symptom of lymphogranulomatosis. It is usually felt in the back, chest or abdomen, and is induced by pressure exerted by the tumour on the roots of the spinal nerves or nerve fibres adjoining it. The disease is often complicated by severe local or generalized itching. In rare cases it appears long before enlargement of the lymph nodes and is the first symptom of lymphogranulomatosis.

The character of changes in peripheral blood in lymphogranulomatosis is mainly determined by the stage of the disease. Anaemia either haemolytic or hyporegenerative develops with the gradual advancement of the disease. The blood leucocyte count is usually normal at the onset of the disease; lymphocytosis is found only at times. Moderate or pronounced leucocytosis (up to $2 \cdot 10^4/1$ μl) is encountered in patients with a generalized disease. The ESR is increased. Lymphopenia develops in the late stages of the disease. The blood eosinophil count is noticeably increased in some patients.

In most cases the disease develops slowly, and over a great length of time is manifested only by enlargement of some one group of lymph nodes. Such patients feel quite well for years sometimes. Splenomegaly is usually the most frequent and often the earliest sign of a generalized process. According to the postmortem findings, involvement of the spleen in generalized lymphogranulomatosis occurs in approximately 70 per cent, involvement of the liver in 50 per cent, and involvement of the lungs in 40 per cent of cases. Involvement of other viscera is encountered much less frequently. Localized affection of the lymph nodes occurs in tumours and infection, as a rule, but does not exclude general diseases of the body listed in Supplement IX-1. The results of clinical examination of patients suffering from involvement of the lymph nodes often do not yield reliable grounds for making the final diagnosis, particularly in patients with tumours arising primarily from the lymph nodes. The final diagnosis of these diseases may usually be established from the results of a long-term follow-up of their course. This method of differential diagnosis, unfortunately, is always hampered by a loss of time. It is common knowledge, however, that the earlier these diseases are treated the more effective is the therapy. That is why in all cases in which the final diagnosis cannot be made from the results of clinical and X-ray examination biopsy of the lymph node must be resorted to.

Such a recommendation is easy to observe when the disease is marked by enlargement of the subcutaneous lymph nodes. In cases in which only the mediastinal or retroperitoneal lymph nodes are enlarged, it is necessary to perform mediastinoscopy and laparoscopy with spot biopsy in order to make the diagnosis. Exploratory thoracotomy and laparotomy are also carried out. Some of the biopsic material is sent for microscopy and some for microbiological examination. A conclusion based on the findings of a single pathological examination is not always conclusive. The diagnosis of lymphogranulomatosis may only be made if Berezovsky-Sternberg's cells are identified in the specimens.

It is particularly difficult to make the differential diagnosis in lymphogranulomatosis marked by primary affection of the mediastinal lymph nodes. For some time the disease is asymptomatic and is often detected for the first time during routine X-ray examination, e.g. in dispensarization. Exacerbations are explained by generalization of the process, its spread to the lungs, pleura and pericardium with the development of pneumonia, pleurisy and pericarditis. Other internal organs (spleen, liver, kidneys) are involved in the later stages of the disease.

The mediastinal lymph nodes are first affected only on one side. Later when the nodes on this side grow to a large size, the process spreads to the contralateral side. As a result of this the shadow of the expanded mediastinum is always asymmetric. The enlarged lymph nodes are usually localized in the anterior and middle mediastinum in accordance with the localization of the bifurcational, paratracheal, and anteromediastinal nodes. The outlines of the shadow are usually polycyclic. The lymph nodes compress the trachea and bronchi causing cough and chest pain. It is our experience that the vena cava superior compression syndrome is an extremely rare occurrence.

Immunoblastic lymphadenopathy was described which began with generalized lymphadenopathy soon joined by fever, profuse sweating and loss of body weight. Enlargement of the liver and spleen was encountered in some cases. The blood globulin content was always increased. The disease tends to follow a progressive course but medication with prednisolone, antibiotics and cytostatics sometimes leads to complete remission. It is assumed that hyperimmune proliferation of B lymphocytes with their transformation to immunoblasts and plasma cells is the underlying factor of the disease.

The diagnosis of lymphogranulomatosis may be made on the basis of findings of routine clinical examination only in the late stages of the disease when simultaneous affection of many systems and organs becomes obvious. At the onset, lymphogranulomatosis usually has to be differentiated from other tumours of the lymph nodes, first and foremost from haematosarcoma.

Other Tumours of the Lymph Nodes

Lymphosarcoma is a tumour of lymphatic origin. It may be primarily localized in the lymph nodes or in different organs (spleen, stomach, intestine, skin, lungs, etc.). In about 65 per cent of cases the disease begins with affection of one group of peripheral lymph nodes. The cervical lymph nodes are involved most frequently. Their affection is threefold that of the axillary, inguinal and retroperitoneal nodes. Primary affection of the mediastinal nodes is encountered in 5 per cent of cases, mainly at a young age.

In most cases the disease sets in insidiously with localized enlargement of the lymph nodes. Generalized affection develops later. The incidence of splenomegaly is half that in lymphogranulomatosis. Generalization of the disease is marked by fever which, like the fever in lymphogranulomatosis, may be irregular, wave-like or hectic. In distinction from lymphogranulomatosis, lymphosarcoma is more frequently attended by autoimmune haemolytic anaemia and thrombocytopenic purpura, and affection of the stomach and small and large intestines is encountered much more frequently. Affection of the kidneys usually in the form of thrombosis of the renal veins with development of the nephrotic syndrome is found in approximately half the patients.

A characteristic feature of lymphosarcoma is extremely rapid advancement of the disease with involvement of the pleura, lungs and intestine and the development of pleurisy and signs of compression of the mediastinal organs and the small or large intestine. Intestinal obstruction and gastro-intestinal bleeding sometimes develop. Involvement of the bone marrow in the process is manifested by thrombocytopenic purpura and lymphocytosis mainly due to an increase in the number of large lymphocytes. In 7.3 to 13.0 per cent of cases of the disease which at first had been mistaken for lymphosarcoma, lymphatic leukaemia developed later. The disease is characteristically highly responsive to X-ray therapy.

Burkitt's lymphoma. In 1958 Burkitt described a new type of tumour marked by affection of the bones, kidneys, liver, heart, salivary glands and the retroperitoneal lymph nodes. The disease is mostly encountered among children. The tumour arises from non-differentiated lymphoreticular cells. The subcutaneous lymph nodes and the spleen are rarely involved. Affection of the gastro-intestinal tract and bone marrow is often encountered in Burkitt's lymphoma like in lymphosarcoma. A leukaemic blood picture appears in the terminal stage of the disease in about one third of the patients. If not treated, the disease progresses rapidly. Death occurs six months after the onset of the disease, on the average. The prescription of cytostatic agents results in remission which lasts longer in patients with the localized form of the disease.

Brill-Symmers' disease. This illness is characterized by a relatively benign course and a tendency to transform to lymphosarcoma. It is usually encountered after the age of 40 and lasts 5 to 15 years.

The disease usually begins with local enlargement of the peripheral lymph nodes; generalized affection of the nodes and splenomegaly are encountered less frequently in the initial period. The spine and other bones of the skeleton are involved in the late stage in approximately 20 per cent of cases. Involvement of the mediastinal lymph nodes in the process leads to the development of the compression syndrome. The retroperitoneal and mesenteric lymph nodes are often enlarged and ascites develops. Fever and cachexia are very rare. Anaemia develops only in the late stages of the disease. The tumour is highly sensitive to X-ray irradiation.

Involvement of the Lymph Nodes in Other Diseases

The clinical picture of tumours arising from the lymph nodes is sometimes very similar to that of lympholeucosis, tuberculosis, sarcomatosis, carcinoma, and systemic lupus erythematosus. The final diagnosis may be established in some cases only from the results of biopsy. Sometimes special methods for staining the specimen must be resorted to in addition to the commonly used stains to identify the cells exactly. In some patients, nodes of the tumour taken from different sites differ in histological structure. In such cases some authors use the collective term 'haematosarcoma', others prefer the term 'non-lymphogranulomatous lymphoma'.

Lymphoid leukaemia. In some cases haematosarcoma resembles lymphoid leukaemia in clinical manifestations (generalized enlargement of lymph nodes, moderate splenomegaly). At the same time a diagnosis of haematosarcoma is at first made in some patients from the findings of lymph node biopsy, but in the later stages the disease terminates as typical lymphoid leukaemia. These two diseases are marked by moderate or pronounced enlargement of lymph nodes in one or more areas of the body and characteristic changes in the bone marrow and peripheral blood. In the wish to emphasize the close resemblance of these two diseases and the possible existence of intermediate forms between them, some authors suggest naming such intermediate cases of the diseases 'leucosarcoma'.

Marked leucocytosis because of an increase mainly in the lymphocyte count is encountered in both diseases, but in lymphoid leukaemia it is permanent, whereas in haematosarcoma it is transient. In haematosarcoma leucocytosis may sometimes be as high

as $2 \cdot 10^4$-$3 \cdot 10^4$ per 1 μl, but nonetheless postmortem examination eventually proves that no lymphoid infiltrates in the liver, spleen and other internal organs typical of lympholeucosis form in the course of the disease.

Most authors point out, nonetheless, that a leucocyte count of more than $3 \cdot 10^4$ per 1 μl is not encountered in haematosarcoma but only if the lymphocytes account for more than 50 per cent of all cells in peripheral blood.

In lymphoid leukaemia the affection of the bone marrow is diffuse, whereas in haematosarcomas only its focal hyperplasia is always found. This very important differential diagnostic sign can be revealed with assurance from the results of trephination biopsy. The widely applied method of bone marrow puncture with Arinkin's needle yields far less reliable results because it does not allow diffuse hyperplasia of the bone marrow to be distinguished from focal hyperplasia.

Sarcoidosis is a systemic disease or a group of morbid conditions with unclear aetiology and pathogenesis. The mediastinal lymph nodes, the lungs and the bronchi are most frequently involved in the pathological process. The disease prevails among females in the prime of life. Almost in one third of the patients the subcutaneous (cervical, axillary, inguinal) lymph nodes are affected simultaneously with the mediastinal lymph nodes. Simultaneous involvement of the liver, spleen, skin, eyes and other organs is sometimes encountered. In most cases the disease begins insidiously and, like lymphogranulomatosis, it is discovered during X-ray examination performed for some other reason. The onset is rarely acute or subacute.

It is extremely difficult to make the differential diagnosis between the initial manifestations of sarcoidosis and those of lymphogranulomatosis. Both diseases usually begin insidiously. Enlargement of the mediastinal lymph nodes is often their only objective sign. In both diseases the appearance of irregular fever is usually associated with the beginning of the generalization of the process. Chest pain and cough are equally pronounced in both diseases. They testify only to compression of the bronchi and nerve structures localized in the thoracic cavity by the enlarged lymph nodes.

In sarcoidosis the subcutaneous lymph nodes rarely have a diameter of more than 1.0-1.5 cm. In lymphoma the lymph nodes are often much larger, but in the initial stages they may be mobile and are no different from the nodes in sarcoidosis in size. Sarcoidosis is usually marked by enlargement of the lymph nodes in the posterior mediastinum, whereas in lymphogranulomatosis the nodes of the anterior and superior mediastinum are enlarged. Bilateral symmetric affection of the mediastinal lymph nodes is often encountered in sarcoidosis, while lymphogranulomatosis is characterized by

asymmetric affection of the lymph nodes. Unilateral affection of the lymph nodes may also be encountered in both diseases. The clinical and X-ray findings on the character of affection of the lymph nodes cannot be accepted as a reliable differential diagnostic criterion. They only point to the greater or lesser probability that the given case is one of the two diseases. Other examination methods should be applied to establish the final diagnosis.

The results of blood tests are positively of assistance in the differential diagnosis of these two diseases. The number of leucocytes in the blood in sarcoidosis is usually either normal or reduced. In lymphogranulomatosis, in contrast, leucocytosis and sharply increased ESR are found during exacerbation. Kveim's test is positive in approximately half of the patients with sarcoidosis, but is always negative in patients with lymphogranulomatosis. The content of calcium in blood and its daily excretion in the urine are often increased in sarcoidosis but are normal in lymphogranulomatosis.

Corticosteroid therapy is usually highly effective in sarcoidosis and ineffective in tumours of the lymph nodes. In sarcoidosis the mediastinal lymph nodes do not change in size after X-ray therapy. Lymphogranulomatous and haematosarcomatous nodes are very sensitive to irradiation. They sharply diminish in size and quite often disappear completely after the first exposures to X-ray radiation. Biopsy or puncture of a lymph node performed during bronchoscopy allows sarcoidosis to be distinguished from primary tumours of the lymph nodes without hesitation.

Metastasis of malignant tumours to the mediastinal lymph nodes is sometimes attended by a clinical picture closely resembling the picture of lymphogranulomatosis and lympho- or reticulosarcoma in manifestations and the rate of progression. The differential diagnosis is difficult in cases in which the localization of the primary tumour is unknown. This happens most frequently in carcinoma of the bronchus with metastases to the mediastinal and cervical lymph nodes.

A primary tumour of the bronchus may be small and the clinical picture of the disease is formed in some cases under the effect of disorders caused not so much by the primary tumour as by the rapid growth of its metastases in the mediastinal lymph nodes. Konchalovsky (1937) called this form of bronchial carcinoma mediastinal. Its clinical manifestations are mainly caused by compression of the mediastinal organs.

The duration of the latent course of the disease is not known. Cough is usually the earliest clinical manifestation of bronchial carcinoma. It is at first dry but later becomes productive. Discharge of mucus or mucopurulent sputum with an admixture of blood is encountered in 16 to 60 per cent of patients. Repeated cytological

examination of the sputum reveals cells of the neoplasm besides red blood cells in many cases. Complaints of malaise and pain on the side of the affection are frequently encountered. Konchalovsky observed moderate or marked fever in half of the patients. According to other authors, fever is encountered much more frequently. A hoarse voice and Horner's syndrome sometimes appear and signs of compression of the trachea, bronchus and oesophagus develop.

Rapidly growing lymph nodes often compress vena cava superior, as a result of which a characteristic syndrome develops composed of moderate or marked thickening of the neck and puffiness of the face. The subcutaneous veins on the neck, upper chest and upper limbs are dilated and involuntarily attract the physician's attention on inspection. The skin of the face and neck is cyanotic. Lymph nodes are often palpated in the subcutaneous fat on the neck and sometimes also in the axillae. They are painless, comparatively small and quite hard. In most cases the nodes of a metastatic tumour are immobile because they are fused with the adjoining tissues.

The entirety of the listed signs forms the syndrome of compression of the mediastinal organs. The rate of progression of this syndrome is determined by the growth rate of the primary or metastatic mediastinal tumour. The rapid growth of symptoms and signs of this syndrome is characteristic of haematosarcoma arising from the mediastinal lymph nodes, metastasis of bronchogenic carcinoma, hypernephroma, melanosarcoma and steroid carcinoma to the mediastinal lymph nodes.

Metastatic mediastinal tumours may be either unilateral or bilateral. Depending on the duration of the process, their diameter ranges from 1 to 2 cm to the size of a newborn's head. Metastases of bronchogenic carcinoma are always unilateral in their initial stages. Involvement of the mediastinal lymph nodes in sarcoidosis, lymphogranulomatosis and haematosarcoma may be either symmetric or asymmetric, but is bilateral, as a rule. Pulmonary tomograms may demonstrate a tendency of the carcinomatous tumour to compress and grow into the adjacent organs. Primary bronchial tumour is usually detected by bronchoscopy and bronchography. If the subcutaneous lymph nodes are enlarged, biopsy of one of them makes it possible to determine the cause of the disease.

Tuberculosis of the lymph nodes. Cough, increased sweating, and protracted fever are often encountered in tuberculosis of the lymph nodes. The disease is mostly encountered among children. The peripheral and the intrathoracic lymph nodes are usually affected simultaneously. Questioning of the patient often reveals contact with a tuberculous patient. The disease may begin abruptly or gradually. The peripheral lymph nodes are small, often fused with each other, and hardly mobile because of periadenitis. Affection of the intrathoracic lymph nodes is usually unilateral.

X-ray examination sometimes demonstrates a single large, intensive, non-homogeneous, round shadow which is called tumour-like or tumorous bronchoadenitis because of its resemblance to mediastinal tumours. The compression syndrome is usually mild. The subclinical character or absence of symptoms of the initial forms of tuberculous bronchoadenitis and the absence, in some cases, of functional disorders in the initial period of the disease suggest some affliction of non-tuberculous aetiology, lymphogranulomatosis or lymphosarcoma.

Lymph nodes affected with tuberculosis are distinguished from lymph nodes in lymphogranulomatosis and lymphosarcoma by a smaller size, harder consistency, poor mobility and a tendency for forming fistulae. Sensitivity to tuberculin is almost always highly increased in patients with tuberculous bronchoadenitis but always diminished in patients with lymphogranulomatosis or lymphosarcoma because of anergy. In tuberculous bronchoadenitis the process is usually unilateral whereas in lymphogranulomatosis it is mostly bilateral. The growth rate of the tumour is also of high differential-diagnostic significance. Extremely rapid growth is characteristic of lymphosarcoma and sometimes of lymphogranulomatosis. Tuberculous bronchoadenitis usually changes in size very slowly.

Treatment with tuberculostatic agents is ineffective in lymphogranulomatosis and lymphosarcoma but proves sufficiently effective in tuberculous bronchoadenitis. In cases presenting a diagnostic problem, the diagnosis is made from the findings of biopsy of a subcutaneous lymph node. Aspiration biopsy of enlarged mediastinal lymph nodes and their puncture during mediastinoscopy or explorative thoracotomy are also conducted. The diagnosis should of course be established before signs of dissemination in the lungs and other organs appear.

Systemic lupus erythematosus. The lymph nodes become enlarged in the early period of this disease as a rule. Generalized enlargement is usually encountered. The lymph nodes are painless to palpation, mobile, and soft. They become enlarged during exacerbations and grow smaller and sometimes are even not palpated at all during remissions. The cervical, axillary, and inguinal nodes are usually enlarged and sometimes the mediastinal nodes.

Enlargement of the lymph nodes in systemic lupus erythematosus is often combined with splenomegaly, anaemia, and moderate or high fever of an irregular type. In some cases the clinical picture may resemble that of tuberculosis, syphilis, lymphoid leukaemia, haematosarcoma, lymphogranulomatosis. The lymph nodes in tuberculosis are distinguished from those in systemic lupus erythematosus by a smaller size and are less mobile and harder. Rapid enlargement is characteristic of lymph nodes in haematosarcoma and lymphogranulomatosis. Moreover, generalized enlargement of the subcuta-

neous lymph nodes in lymphogranulomatosis is always combined with mild enlargement of the mediastinal nodes. The character of the lymph node affection is determined more precisely from the results of biopsy.

Syphilis. Generalized enlargement of the lymph nodes is encountered in syphilis. Regional inguinal lymphadenitis is an indispensable sign of primary syphilis. Secondary syphilis is marked by involvement of all the groups of the body's lymph nodes. Particular diagnostic significance is attached to enlargement of the occipital lymph nodes because in an adult they are also permanently enlarged (besides syphilis) only in lymphoid leukaemia and in ulcero-purulent diseases of the skin of the scalp.

In syphilis the lymph nodes are small, painless, mobile, and of a dense consistency. They may stay enlarged six to eight months after all the other signs of secondary syphilis disappear. Syphilitic adenopathy is easily recognized when there are other signs of secondary syphilis. In a later period the nature of lymphadenopathy is confirmed by positive serological tests for syphilis.

Tumours and Cysts of the Mediastinum

The subcutaneous lymph nodes are always accessible to biopsy and the character of their affection may therefore be determined soon after the appearance of adenopathy. It is much more difficult to reveal the cause of isolated enlargement of the intrathoracic lymph nodes. They are often mistaken for benign tumours of the mediastinum, aneurysm of the aorta or an enlarged retrosternal thyroid. Errors in preoperative diagnosis of mediastinal lesions come up to 27.9 per cent.

Neurogenic tumours. Primary and metastatic tumours of the mediastinal lymph nodes often have to be distinguished from neurogenic tumours which may be either benign or malignant. They arise from different cell components of the nerve ganglia and membranes of the sympathetic trunk. The tumour is usually oval and is found in the costovertebral angle. In most cases it is at first localized outside the posterior mediastinum but growing gradually spreads to it. In rare cases a neurogenic tumour arises from the vagus, phrenic or some other nerve in the mediastinum. The tumour occurs on the right side as a rule and sometimes grows to a considerable size. In one of our cases it occupied almost half of the right pulmonary field and caused distortion of the spine.

The disease sets in insidiously and follows a latent course for a long time or the patient makes uncharacteristic complaints of pain in the chest or back. Even large tumours which cause displacement of the mediastinal organs often induce only a sensation of

indefinite poorly localized pain in the chest. In most cases neurogenic tumours are disclosed by chance during X-ray examination for some other reason.

The tumour is usually oval and has a clearly demarcated even or wave-like boundary. Its shadow is almost always homogeneous and only in rare cases small foci of calcification are seen in the tumour.

Neurogenic tumours arising from the root of a spinal nerve merit special attention. Such a tumour is partly localized, as ordinarily, in a costovertebral angle and partly in the cerebrospinal canal. Both parts are joined by means of a narrow isthmus localized in the intervertebral foramen. The whole tumour is shaped like an hour glass. In the clinic, such tumours are usually first manifested by pain in the spine and signs of compression in the upper thoracic segment of the spinal cord. Radiographs demonstrate in some cases usures of the vertebrae and ribs and dilatation of the intervertebral space. This form of neurogenic tumour may be considered when intercostal neuralgia, paresis of the lower limbs and other signs of affection of the spinal cord appear in a patient who has a solitary tumour in the posterior mediastinum.

Benign neurogenic tumours grow very slowly. They never grow into the adjacent organs, e.g. the bones or lungs. Even malignant hourglass tumours are capable of causing usures of a bone but do not grow into it. Malignant tumours grow much faster than benign tumours. The difference in the rate of growth probably explains why signs of compression of the mediastinal organs never occur in benign tumours but develop often in malignant neurogenic tumours.

Dermoid cysts and teratomas are somewhat less frequent than neurogenic tumours. In most cases they are localized in the anterior mediastinum directly behind the sternum, usually to the right of its midline. They are an exceptionally rare occurrence in the posterior mediastinum. Like many other embryonal developmental abnormalities, they produce no signs for a lengthy period of time and are usually disclosed by chance on X-ray undertaken for some other reason. With time, dermoid cysts begin growing gradually and exert pressure on the adjacent organs.

In approximately 75 per cent of cases the disease begins insidiously with shortness of breath and pain in the chest. Dyspnoea at first appears only during physical exercise but later it becomes permanent. Sometimes it develops into paroxysmal dyspnoea displayed by attacks of dry or productive cough. These attacks are explained by pressure exerted on the adjacent bronchus by the growing dermoid cyst. Stenosis of the bronchus may be attended by pneumonia.

The disease is often manifested for the first time by complications. Infection of the cyst, its rupture into the bronchus, pneumonia, and the formation of usures in the sternum are usually encountered.

Although these complications occur suddenly, detailed questioning reveals in most cases their association with long existing chest pain, shortness of breath, and paroxysmal dyspnoea.

X-ray examination discloses a solitary rounded shadow with clear outlines in the anterior mediastinum. Sometimes its boundaries are irregular. The capsule of the cyst is often calcified and resembles that of a hydatid cyst. Dense inclusions are often seen in the shadow; these are calcareous or bony structures of various size and shape. Dermoid cysts and teratomas are almost never complicated by the compression syndrome, but often adhere to the wall of the aorta and make pulsatile movements together with it. In distinction from the pulsatile movements of the aorta, their movements are transmissive in character.

Dermoid cysts and teratomas may become infected, degenerate or develop into a malignant form. The occurrence of complications changes sharply the clinical course of the disease. Fever sets in, chest pain intensifies, metastasis of the tumour to the cervical and mediastinal lymph nodes occurs, and signs of the compression syndrome increase rapidly. The clinical pictures developing in such cases differ sharply. The thoroughness of the patient's examination before the development of the complications makes the differential diagnosis less difficult.

Intrathoracic goitre may arise from the main thyroid or from small accessory glands separating from it in the embryonal period. A retrosternal goitre forms in the first case, and a mediastinal goitre localized behind the sternum, trachea or oesophagus in the second. The disease may be marked by thyrotoxicosis or thyroid deficiency. Goitre arising from the accessory thyroid glands and nodular goitre undergo malignant degeneration. It is not difficult to make the diagnosis of a retrosternal goitre if part of it is palpated on the anterior surface of the neck, for instance, when the patient swallows, coughs or strains.

The thyroid is situated on the trachea and even a small goitre may therefore lead to displacement and stenosis of the trachea. The trachea is especially compressed by goitre found behind the trachea and oesophagus. Its compression is attended by cough and dyspnoea which are sharply intensified when the head is flung back or turned. Stridulous breathing interrupted by paroxysmal dyspnoea develops in severe tracheal stenosis. Compression of the oesophagus and recurrent laringeal nerve is encountered much less frequently.

Intrathoracic goitre is seen on X-ray as a moving shadow usually in the upper part of the anterior mediastinum or, in rare cases, in the posterior mediastinum. The shape of the shadow may vary, but its outlines in non-complicated goitre are always clear. A shadow with unclear boundaries is encountered in malignant goitre and when an inflammatory process develops around the gland. The

shadow of the goitre is usually homogeneous but sometimes dense inclusions are seen in it which are caused by the deposition of calcium salts in the nodes of the gland and the formation of cartilaginous and, in rare cases, bony tissue.

The size, shape, and functional state of the thyroid may be successfully demonstrated by scanning. Both the retrosternal part of the gland and the occasional small glands localized behind the sternum or in the anterior mediastinum are seen.

Malignant degeneration of goitre is recognized by its nodular surface, immobility, the appearance of hard foci in it, pain which is usually referred to the lower jaw and ear, by the rapid advancement of the compression syndrome, by the appearance of fever, leucocytosis, and by metastasis to the lymph nodes of the neck and mediastinum.

Tumours of the thymus. All types of benign (fibroma, lipoma, myxoma, cyst) and malignant (lymphosarcoma, carcinoma, etc.) tumours of the thymus are generally designated 'thymoma'. Most malignant tumours of this gland are haematosarcomas. They are marked by rapid growth with the development of the compression syndrome, growth into the adjacent organs, and fever. Death occurs a few months after the appearance of the first symptoms. Benign tumours of the thymus are distinguished by slow growth and are a chance finding in examination of the patient for some other reason. Carcinoma of the thymus grows much slower than haematosarcoma but metastasis to the mediastinal and cervical lymph nodes occurs at an early period and the condition is complicated by the compression syndrome within a quite short period.

The predominant symptom in the clinical picture of malignant thymoma in the early period is dyspnoea which forces the patient to sit up in bed. Attacks of coughing and paroxysmal dyspnoea develop in attendance. Pain is felt in the upper thorax either continuously or in attacks. In the latter case it is sometimes mistaken for anginal pain. The thymus is localized in the upper part of the anterior mediastinum. It is richly surrounded by fatty tissue so that the above-listed signs and symptoms of compression of the trachea, main bronchi, and nerves usually appear when the tumour has already grown to a considerable size. Signs of compression of vena cava superior appear in a later stage of the disease: puffiness and cyanosis of the face, thickening of the neck with swelling of the veins, and dilatation of the subcutaneous veins, mainly those on the right arm and anterior surface of the chest. A tumour occupies the inlet of the chest in such cases and some of its nodes are palpated above the sternal manubrium, in the supraclavicular fossae, and on the neck. Protrusion of the upper chest and growth of the tumour into the sternum are sometimes encountered.

X-ray demonstrates an additional shadow, usually symmetrical,

in the anterior mediastinum. Benign thymoma is always clearly outlined and with growth it compresses the adjacent organs but does not grow into them. Infiltrative growth with involvement of the pleura and pericardium is characteristic of malignant thymoma, and the condition is manifested by the clinical syndromes of pleurisy and pericarditis. The clinical picture of malignant thymoma is like that of mediastinal haematosarcoma in most cases and is often mistaken for it.

Mediastinal cysts. Benign tumours of the mediastinum (thymoma, teratoma, etc.) often have to be differentiated from pericardial cysts, which cause no subjective sensations in most cases. Cysts of the pericardium are localized in the lower anterior mediastinum, usually in the region of the right cardio-diaphragmatic angle. They have an oval shadow which alters slightly during deep respiration.

A hydatid mediastinal cyst is such a rare occurrence that some authors suggest that such a diagnosis should be made only when the presence of hydatid cysts in other organs has also been established (Lukyanchenko, 1958).

Aneurysm of the aorta. In most cases the diagnosis of aneurysm of the aorta is made by means of the commonly used examination methods. Particular diagnostic significance is attached to a history of syphilis, positive serological tests for syphilis, a continuous murmur on the aorta, dilatation and usually intensified pulsation of one of its segments. Aortitis attendant to the aneurysm is usually manifested by subfebrile temperature, leucocytosis and increased ESR. In cases in which the aneurysm is a complication of syphilitic aortitis, the other manifestations of syphilis (Argyll Robertson pupil, loss of tendon reflexes, gummatous lesions of the bones) aid greatly in establishing the diagnosis.

Aneurysm of the ascending aorta may be asymptomatic for a long time, but growing gradually it begins to press on the sternum and the adjacent mediastinal organs. Aneurysm of the descending aorta causes erosion of the vertebrae. The aneurysm stimulates the roots of the spinal nerves and thus induces sharp pains in the chest. Pressure exerted on the trachea and main bronchi causes cough and shortness of breath, pressure on the left recurrent laryngeal nerve leads to loss of voice, while pressure on the oesophagus causes dysphagia. The other manifestations of aneurysm of the aorta (e.g. the X-ray sings) may also resemble closely the manifestations of malignant and benign mediastinal tumours.

It is particularly difficult to distinguish aneurysm of the aorta from benign tumours of the mediastinum which are characterized (like the aneurysm) by slow growth. An enlarged lymph node may be the only manifestation of lymphogranulomatosis for a lengthy period of time, in which case it is often mistaken for aneurysm of

the aorta. The abnormal shadow in aneurysm of the aorta, most benign tumours, and lymphogranulomatosis is evenly outlined and has a homogeneous structure. If the aneurysm is not thrombosed, expansive pulsation of its outlines distinguishes it from tumours. Most aneurysms, unfortunately, contain parietal thrombi as a result of which they do not pulsate and the continuous murmur audible over them changes to systolic.

Haemoptysis is among the late, but important signs of aneurysm. It is encountered in approximately 25 per cent of cases of aneurysm of the aorta and is not found in benign mediastinal tumours. Lymphogranulomatosis is sometimes complicated by haemoptysis, but this happens only in the late stages of the disease when it is easily distinguished from an aneurysm by the multiple affection of the lymph nodes in the mediastinum and sometimes also on the neck.

Aortography is the most reliable method for identification of an aneurysm. If this cannot be carried out for some reason, attention should be focused on the presence of usures in the bones adjacent to the abnormal shadow and the symmetric pattern of the shadow. Aneurysm of the aorta destroys the adjacent bone and is always localized either in the right or in the left half of the mediastinum. The centre of an abnormal shadow produced by a mediastinal tumour is always localized within the limits of the median shadow.

Supplement IX-1

Causes of Lymph Node Enlargement

1. Tumours arising from the lymph nodes.
   - Lymphogranulomatosis.
   - Lymphosarcoma.
   - Burkitt's lymphoma.
   - Brill-Symmers' disease.
2. Affection of lymph nodes in other diseases.
   - Lymphoid leukaemia.
   - Sarcoidosis.
   - Metastasis of malignant tumour to the lymph nodes.
   - Tuberculosis of the lymph nodes.
   - Systemic lupus erythematosus.
   - Syphilis.
3. Tumours and cysts of the mediastinum.
   - Neurogenic tumours.
   - Dermoid cysts and teratomas.
   - Intrathoracic goitre.
   - Tumours of the thymus.
   - Mediastinal cysts.
4. Aneurysm of the aorta.

Chapter X

Fever of Unknown Origin

Body temperature is a physiological body constant. Fever, i.e. elevation of body temperature under the effect of a disease, may be of a short or long duration. It may occur simultaneously with the other signs of the disease (e.g. in acute lobar pneumonia) or develop in attendance to them some time later (e.g. in myocardial infarction) or long before them. In the last case, fever predominates in the picture of the disease for some time or is even its only obvious clinical manifestation.

Muscular exertion is quite often attended by a rise in body temperature. Short-term hyperthermia occurring as a regular phenomenon in children under the effect of playing in fresh air and hyperthermia caused by the simultaneous action of exercise and high environmental temperature are generally known conditions. Hyperthermia in such cases is distinguished by its briefness. The causes are obvious. It disappears soon after the action of the factors causing it ceases. Many chronic non-infectious diseases are marked by short-term or long-term increase in body temperature. The cause of this fever is established in most cases after clinical examination of the patient which takes about two, rarely three, weeks.

The term 'fever of unknown aetiology' is used in cases in which body temperature is elevated continuously for a period longer than that stated and when the results of clinical, X-ray, bacteriological, and other special methods of examination carried out within that time provide no grounds for making the final diagnosis of the disease.

Long-term fever is one of the most reliable signs of an organic disease. Patients are also well aware of this. Some of them demonstrate at times extreme inventiveness in the methods for raising artificially the results of body temperature measurement for various motives. Much time and energy are sometimes needed to reveal the causes of this artificial fever. All artificial fevers are characterized by the following signs: the absence of the usual daily fluctuations in body temperature and distortion of the usual relationships between the fever and the pulse and respiratory rates.

It is particularly difficult to distinguish fever caused by a disease from disorders of body temperature regulation known as *habitual*, or *constitutional, hyperthermia.* It is mostly encountered among young women with signs of the asthenic syndrome. Arterial hypo-

tension and vasomotor lability are found simultaneously with hyperthermia in these patients. Diffuse hyperaemia of the face, neck, and upper part of the chest occurs even in mild inflammation. Body temperature is usually subfebrile but in situations calling for exertion of all the body's physical and mental forces it stays at 37.8-38°C and may even rise above this level several times during the day.

In our experience, boys, like their mothers, developed long-term fever for the first time during intensive study for their school-leaving certificate.

To identify the causes of hyperthermia such patients are admitted to different clinics where they are examined by many different methods and various diagnoses are made. A substantiated opinion concerning the cause of hyperthermia may evidently be made only from the results of a follow-up of many years.

Long-term fever with no clinically obvious signs of affection of some organ occurs in very many diseases: those that are encountered most frequently and are most important are listed in Supplement X-1. Fever of a long duration develops not in some unusual diseases as a rule, but in diseases commonly encountered in the practice of internists and following an atypical course. Subacute bacterial endocarditis, for instance, is marked in most cases by fever, anaemia, nephritis, splenomegaly, and other generally known signs. In some cases fever predominates in the clinical picture of this disease for several weeks and is attended only by an atypical systolic murmur. The cause of long-term fever in leukaemia can sometimes be identified only after sternal puncture.

The great number of factors which may induce fever make it impossible to suggest a unified scheme of the examination of patients. In our experience most fevers of unknown aetiology proved to be of infectious origin. A tumour is a much less frequent cause of long-term fever. Fevers of a long duration induced by a group of diseases known as collagenosis are still rarer. The diseases mentioned account for 90 to 95 per cent of all fevers whose aetiology cannot be identified in some cases for a very long time. Long-term fever of some other origin is a very rare occurrence; it is usually encountered once in several years.

In a case of fever of unknown origin it is necessary to focus particular attention on questioning the patient. Repeated taking of the medical history may disclose the role of the patient's occupation and epidemiological factors to which close attention was not drawn during the first talk. It is important to find out whether or not the patient contacted animals or birds, special attention should be paid to the history of diseases, operations, and infections widely encountered in the patient's place of residence or in places which he had visited as a tourist. The physician must ask the patient what drugs he had taken recently and whether or not he had suffered from drug

intolerance in the past. On repeated physical examination it is necessary to look for foci of latent chronic infection which may be manifested by the occurrence of new foci of pain, swelling, and disturbances in the function of the affected organs. Repeated immunological tests and repeated X-ray and other special methods of examination are necessary because they yield valuable information.

It is very important to have a clear idea of the possibilities and limitations of the methods of examination that are employed. This applies in particular to the interpretation of the results of immunological tests. To avoid erroneous results, the most responsible tests should be repeated. A positive Wassermann reaction, for instance, must be confirmed by the results of the test for Treponema pallidum immobilization test. Blood cultures for isolating the causative agent in its pure form must be repeated, e.g. every hour for several hours. The results of a single culture are not reliable.

The diagnostic value of the method of trial therapy in fevers of unknown aetiology is very limited. The use of antibiotics, steroid hormones and other agents only complicates the already difficult diagnostic problem. Non-specific improvement in the general condition after the application of steroid hormones may only harm the patient in some cases, e.g. in a case of subdiaphragmatic abscess. If it is nonetheless decided to carry out trial therapy, the drug should be chosen with great care and, which is no less important, its doses and the duration of medication determined. The prescription of prednisolone (in cases with suspected systemic lupus erythematosus) or rifamycin (when tuberculosis is suspected) may yield diagnostic information if the drug is used in a sufficiently high dose and for a sufficient period of time.

Biopsy of various organs has to be performed sometimes to identify the cause of the fever. In conducting this examination it is not sufficient to simply know the possibility of each method, it is also necessary to take into account the specific features of the presumed pathological processes; for instance if Crohn's disease is suspected aspiration biopsy must be conducted in strictly defined segments of the intestine and not at random, and even mucosal areas which seem normal in appearance must be examined histologically without fail because the most characteristic changes in this disease develop in the deeper lying parts of the intestine rather than in the mucous membrane. Sternal puncture proves insufficiently informative in some cases and must be replaced by trepanobiopsy.

Long-term fever with no concomitant changes in the function of an organ is a particularly regular occurrence in tuberculosis, lymphogranulomatosis, haematosarcoma, and diffuse diseases of the connective tissue. In all of these cases, the pathological process is usually localized in the abdominal cavity, e.g. in the wall of the

small intestine, the biliary tract, the mesenteric lymph nodes and in the retroperitoneal space.

In some cases the rise in body temperature is asymptomatic, in others it is attended by a chill, convulsions, and delirium. The term chill, or rigor, designates a condition in which the patient experiences an inner shivering and a sensation of cold which are not relieved even by heating pads or covering with a warm blanket. The objective signs are pallor of the skin, 'goose-flesh', and clearly visible involuntary muscular tremor which is sometimes so severe that the patient cannot utter a word and his teeth 'chatter'. During the chill (which rarely lasts more than 30 minutes) body temperature is elevated by 2 to 4°. The chill is replaced by a feeling of heat which is often followed by increased sweating. A more or less noticeable leucopenia is always found during the chill and for a short period after it ceases.

A herpetic eruption often appears during fever. It is caused by herpex simplex virus which is activated by the fever. This eruption is so common in some fevers that its appearance is accepted as a diagnostic sign of the disease, e.g. in pneumococcal pneumonia or meningococcal meningitis. Fevers, artificial among others, are often attended by proteinuria which disappears soon after body temperature falls to normal level. High fever is sometimes complicated by delirium which is a particularly regular occurrence in old persons and in individuals suffering from alcoholism.

Fevers of unknown aetiology occur suddenly in some cases and insidiously in others. Sudden high fever is of infectious origin as a rule, fever that sets in unnoticeably is usually caused by tumours and other diseases following a chronic course. Besides the acute onset mentioned above, the following signs are characteristic of infectious fevers: chills during which body temperature usually rises to 39-41 °C, general weakness, headache, pain in the muscles and joints, enlargement of the lymph nodes and spleen, nausea, vomiting or diarrhoea, meningeal symptoms, leucocytosis or leucopenia, pain in the throat and eyeballs. None of these signs are specific of any chronic disease. Some of them are encountered also in diseases which, according to modern conceptions, are not related to infections.

Chills occur in bacterial, virus, parasitic, rickettsial and other infections. They develop in about one hour after the causative agent of a disease or any foreign protein enters the blood. Study of the number and character of chills in different diseases is of definite diagnostic significance. Diseases characterized by a single chill and those marked by a series of chills may be schematically distinguished.

A single chill appears at the beginning of many infectious diseases. It is especially characteristic of diseases with a sudden onset,

Shaking chill is a constant initial sign of acute lobar pneumonia. It is always encountered after transfusion of incompatible blood. Acute infections of the urogenital tract very often begin with a chill. A single chill is occasionally encountered in serum sickness.

A series of chills occurring during a disease are of much higher diagnostic significance. They are encountered in a relatively small number of diseases listed in Supplement X-2. Multiple chills usually occur in infectious diseases. When clinical and X-ray methods of examination fail to reveal disorders in the functioning of an organ, the cause of the chills may sometimes be identified by means of blood, bile or urine cultures and by examining gastric irrigation waters. It is advisable to take the blood sample for the culture about one hour before the expected chill or when the body temperature has risen. Positive results are much less frequent if the blood is collected after body temperature drops. At least three blood cultures should be made within 24 hours.

Repeated chills in malaria are distinguished by strict regularity. They may develop daily, every other day or at intervals of two days. The period of chills is replaced by a period of fever followed by profuse sweating. This characteristic triad is encountered in many other diseases, among which are those of non-infectious origin too, e.g. carcinoma of the lung, hypernephroma, leucosis, and lymphogranulomatosis. Chills occurring in acute leucoses are evidently associated with concomitant bacterial or fungus infection. It is possible that such is also the origin of chills in carcinoma and lymphogranulomatosis.

Repeated chills always occur in all forms of sepsis. In puerperal sepsis they are usually accompanied by sanguineous foul-smelling secretions from the vagina; anaemia may develop later. Repeated chills with the subsequent appearance of heart murmurs are characteristic of acute and subacute bacterial endocarditis. Multiple septic embolisms appear in the later stages of these diseases and may themselves become foci of suppuration and the cause of new chills. Multiple chills (usually occurring several times within 24 hours) are sometimes among the most prominent and early manifestations of clinical septicaemia. Chills with subsequent fever and profuse sweating always occur in pyaemia. Like leucocytosis, they are related to the constant signs of this type of sepsis. Subdiaphragmatic abscesses and acute osteomyelitis, which are frequent complications of sepsis, are manifested by repeated chills.

Acute pyelophlebitis and the less frequently encountered chronic form of the disease are marked by repeated chills as a rule. They are usually complications of purulent appendicitis or some other inflammatory disease of the abdominal organs. Intravascular infected thrombi form in the zone of the inflammation, they disintegrate with the formation of many septic emboli. These emboli enter the

liver in the blood and cause the development of many small abscesses in it. Pain in the right hypochondrium, hepatomegaly and, often, jaundice develop soon in attendance to the chills in such cases.

Repeated chills are often encountered in inflammatory diseases of the urogenital system. They occur usually simultaneously with abnormalities in the urine: pyuria, haematuria, proteinuria, and disorders of micturition. In inflammatory diseases of the gall bladder and biliary tract chills occur together with an enlarged gall bladder, jaundice and enlarged and tender liver. These patients often have a history of cholelithiasis and recurrent attacks of biliary colic. In such cases jaundice may be a consequence either of obstruction of the biliary ducts or the formation of multiple abscesses in the liver. Amoebic abscess of the liver has a similar clinical picture.

Recurrent chills are often encountered in inflammatory diseases of the lungs: bacterial and other forms of pneumonia, in pulmonary abscesses, bronchiectases, congenital cysts, tuberculosis and purulent pleurisy. Shaking chills are among the characteristic manifestations of erysipelas. Recurrent chills are always evidence of some severe disease and should always be a reason for the most scrupulous diagnostic examination of the patient.

General Infection

Sepsis

Sepsis is a severe infectious disease marked by the multiplication of its causative agent in the blood or in the tissues. In the latter case metastasis of the infection to other organs and tissues occurs from time to time. Toxicosis and high fever predominate in the clinical picture of sepsis. Recurrent chills with profuse sweating occur several times a day in some cases. High leucocytosis with a shift to the left and increased ESR develop simultaneously with the fever. This formidable clinical picture develops in most cases in association with a furuncle, carbuncle, after delivery, pricks and cuts of the finger, tooth extraction and other manipulations during which the skin or mucous membranes are damaged. In such cases sepsis may be presumed from the first days of the disease.

When bacteria multiply in the blood the condition is called **septicaemia.** Sepsis marked by the formation of metastatic abscesses is called **pyaemia.** These abscesses usually form in the subcutaneous fat and in the lungs. Pyaemia begins abruptly, as a rule. Its clinical picture is composed of hectic fever with recurrent chills, leucocytosis, and embolic abscesses. Multiple embolisms in the lungs lead

to the development of infarction pneumonia which is often complicated by abscess or purulent pleurisy. Abscesses in the soft tissues and joints are manifested by the classical signs of inflammation: local tenderness, swelling and hyperaemia, increased local temperature and impaired function.

An internist most often has to deal with septicaemia in which even the most thorough examination of the patient and the most detailed questioning fail to disclose the porta of entry of the infection. That is why a diagnosis of some acute infectious disease is often made at first and only later, with the appearance of characteristic chills and marked toxicosis, sepsis is presumed and blood cultures are made. They are performed both for establishing the diagnosis and for testing the sensitivity of the causative agent to antibiotics. It is advisable to take the blood for the culture 30 to 60 minutes before the expected peak of the temperature curve or during the fever. Bacteraemia is often short-lived and it is therefore recommended to take three to five blood samples, 20-25 ml each, during the day. Some authors advise that three blood samples should be taken daily for three or four days.

Short-term bacteraemia often develops in a healthy person also. It is always encountered after tooth extraction, tonsillectomy and delivery. It is often found after cystoscopy and proctoscopy, and during acute inflammatory diseases of the respiratory tract and the small and large intestine. In such cases bacteraemia in a healthy person is short-lived. In patients with congenital and acquired heart and vascular diseases, the bacteria settle on the affected valve or at the site of the defect in the parietal endothelium and form a colony. Bacterial endocarditis is a disease occurring as a consequence of colonization of the heart valves, parietal endocardium or the vascular endothelium by bacteria, fungi or other pathogenic organisms.

Acute or **subacute bacterial endocarditis** develops. The latter is usually called endocarditis lenta. The clinical picture of acute bacterial endocarditis is similar to that of septicaemia. The appearance of a systolic murmur in septicaemia is accepted as sufficiently convincing evidence in favour of colonization of the heart valves by the causative agents of sepsis. Acute bacterial endocarditis usually develops in patients with no signs of an organic disease of the heart. Endocarditis lenta is mostly encountered in patients with congenital and acquired heart diseases.

Endocarditis lenta is a most frequent complication in mitral heart disease with prevalence of insufficiency and in aortic heart diseases (aortic insufficiency and a bicuspidal aortic valve which usually has a clinical picture of aortic stenosis). Endocarditis lenta often develops in the aortic valve distorted by a syphilitic process. It is hardly ever encountered in atrial septal defect but is a frequent complication of ventricular septal defect, patent ductus arteriosus,

coarctation of the aorta and arteriovenous aneurysm. In the last three cases it would be more correct to speak of bacterial endarteritis. The term 'bacterial endocarditis' is applied conditionally in regard to these diseases.

Endocarditis lenta sets in insidiously in most cases, with fever which is soon joined by signs of a heart lesion. Embolisms in the vessels of the systemic or pulmonary circulation develop in the later stages of the disease and sometimes predominate in the picture of the disease.

Fever is the most constant sign of bacterial endocarditis. Chills with elevation of temperature to 40-41 °C followed by profuse sweating are evidence of a more acute and severe course of the disease. Headache is often experienced during the elevation of temperature and sometimes it is the only complaint made by the patient. In milder cases the periods of high temperature (continuous, remittant or of an irregular type) are periodically replaced by periods of subfebrile fever the duration of which rarely exceeds one or two weeks. A fever reaction is never encountered in patients with signs of chronic renal insufficiency and is very rarely encountered in patients with normal renal function. Anaemia is also among the early syndromes of bacterial endocarditis. Fever and anaemia are evidently the main causes of the patient's general weakness and easy fatiguability. Anorexia and rapidly progressing loss of weight occur as a rule.

The clinical picture of bacterial endocarditis does not differ from that of septicaemia until the heart becomes involved, which in typical cases is manifested by mitral or aortic insufficiency. In a patient with an earlier existing heart disease, bacterial endocarditis leads to the appearance of new murmurs, changes in the character, force and timbre of the old murmurs, and the appearance of peripheral signs of aortic insufficiency. Colonization of the tricuspid valve induces no changes in the auscultative picture of the heart for a long time. In this localization of bacterial endocarditis a systolic murmur usually appears simultaneously with signs of heart failure (enlargement of the liver, dilatation of the subcutaneous veins on the neck, oedema of the subcutaneous fat).

The late signs of bacterial endocarditis are as follows: characteristic colour of the skin ('cafe au lait'), clubbed fingers, and multiple embolisms which are usually found in the vessels of the skin and mucous membranes in the fundus oculi, kidneys, spleen and brain.

Septic emboli in the skin and mucous membranes (Lukin-Libman's sign) have the appearance of petechiae with a white centre. They are usually found in the conjunctiva of the lower eyelid and the oral mucosa. Petechiae with a white centre are also detected in the retina. Petechiae in the conjunctiva of the lower eyelids are of highest diagnostic significance. They may be single or may appear one after the other in small series.

Libman claims that septic embolisms into the skin (Osler's nodes) are pathognomonic signs of endocarditis lenta. They are commonly found on the pads of the fingers and toes, in the skin of the thenar and hypothenar, and on the soles.

Involvement of the kidneys in bacterial endocarditis is manifested by infarcts and localized or diffuse glomerulonephritis. Affection of the kidneys is detected much earlier than affection of other organs. Proteinuria appears in every and haematuria almost in every case of bacterial endocarditis. The nephrotic syndrome and chronic renal insufficiency occur in the late stages of the disease.

Enlargement of the spleen is found in approximately two thirds of bacterial endocarditis cases. This is a late sign of the disease and its development is attributed to infarcts in the organ. We likewise encountered abscesses of the spleen in our practice.

Affection of the central nervous system is among the frequent complications of bacterial endocarditis. Embolization of the cerebral vessels is attended by strokes, the most frequent underlying factor of which is obstruction of the large arteries and a less frequent factor rupture of mycotic aneurysms. The clinical picture in such cases comprises fever and signs of meningitis and encephalitis.

Bacterial endocarditis of the tricuspid valve and patent ductus arteriosus are attended by embolisms of the pulmonary vessels with the formation of infarcts usually simultaneously in both lungs. These infarcts tend to become complicated by pneumonia, abscess and, in rare cases, by pleurisy. The blood leucocyte count is normal in more than half the cases. Leucocytosis appears only in cases of multiple embolisms or in association with pulmonary infarcts. An increase in the blood gamma globulin content and high ESR are characteristic signs.

Errors in the diagnosis of bacterial endocarditis are made mainly because the constant syndromes of this disease (embolisms into different vascular regions of systemic and pulmonary circulation) are marked by a great variety. In clinical signs they cannot be differentiated from pneumonia, stroke, encephalitis, heart failure, chronic renal insufficiency and other syndromes with which the physician is more familiar. Long-term fever is considered the most frequent and earliest sign of bacterial endocarditis, but in many cases this disease may begin insidiously and be marked only by bouts of subfebrile temperature. Cases of bacterial endocarditis without fever are encountered rarely. In about 20 per cent of cases the blood culture proves to be sterile. This happens because of the great variety of causative agents each of which grows only on strictly definite media.

A systolic murmur is also not an obligatory sign of endocarditis because the colonies of the causative agent may be localized on the

parietal endocardium or on the endothelium of arteries or arteriovenous anastomoses.

In mild cases the diagnosis of endocarditis lenta is based on the detection of long-term fever, septic embolisms in the skin, kidneys and brain and bacteraemia in a patient suffering from some congenital or acquired heart disease. In cases that present a diagnostic problem, the diagnosis is based on the results of a follow-up of the clinical course of the disease. The correct diagnosis in such cases is often delayed because the more or less typical complex of syndromes (anaemia, splenomegaly, clubbed fingers, nephritis) develops only in the late stages of the disease.

In most cases bacterial endocarditis begins with fever and its timely diagnosis may therefore be made only when the search for the causative agent begins and ends long before irreparable complications (heart failure, chronic renal insufficiency or cerebral circulatory disorders) develop. The diagnosis may be made in good time if the possibility of endocarditis lenta is considered in every case of fever of unknown origin and if blood cultures are made. The possibility that the patient has endocarditis lenta must be regarded as highly probable when fever is encountered in a patient with an organic heart disease.

Since endocarditis lenta most frequently develops in patients with a congenital or acquired heart disease, it usually has to be differentiated from recurrent rheumatic carditis with heart failure complicated by pulmonary infarct and perifocal pneumonia. In our practice we often had to distinguish it from cerebral circulatory disorders and from chronic glomerulonephritis.

Friedberg (1966), Bauer (1967) and other authors indicate that they often had to differentiate endocarditis lenta from systemic lupus erythematosus. We never came up against this kind of difficulty, probably because the contingents of patients differed greatly.

Fever in a patient with rheumatic heart disease is usually first attributed to influenza or some other acute respiratory infection. If body temperature eventually reduces to subfebrile levels spontaneously or under the effect of antibiotic therapy commonly used in such cases, exacerbation of rheumatism is presumed in a patient. Vigorous antirheumatic therapy proves ineffective and heart failure develops in the patient which also does not respond to therapeutic measures. The situation described is a frequent occurrence, particularly in patients given steroid hormones. Heart failure gradually gains predominance in the picture of the disease. Shortness of breath is joined by hepatomegaly and oedema, infarcts form in the congested lungs which are complicated by perifocal pneumonia.

Identification of the true cause of the disease is a very difficult task in some cases. Results are more reliable if the severity of disorders in myocardial conduction and excitation are appraised in

the early stages of the disease, and sequence of the appearance of fever and heart failure in the later stages. Other signs may greatly help too, but in contrast to those listed above, they are inconstant.

In most cases of rheumatic carditis, the diffuse affection of the myocardium leads to disorders of heart automatism and conduction. Delayed atrioventricular conduction is considered a particularly characteristic sign. Disorders of intraventricular conduction are much less frequent. The severer the rheumatic carditis, the more frequent the ventricular and atrial extrasystole and other disorders of the heart rhythm. Cardiac fibrillation is among the frequent disorders of the heart rhythm in mitral valvular diseases marked by signs of heart failure. These disorders of rhythm in exacerbations of rheumatic carditis always precede heart failure.

Endocarditis lenta is usually unattended by disorders of the heart rhythm. It is our experience that delayed atrioventricular conduction is a rare occurrence in this disease, while disorders of intraventricular conduction are extremely rare. The absence of disturbances of cardiac excitation and conduction in doubtful cases should be interpreted as a sign in favour of bacterial endocarditis.

High differential diagnostic significance should also be attached to the sequence in the appearance of the signs discussed above. In exacerbation of rheumatic carditis disorders of cardiac conduction and excitation develop at the beginning of exacerbation and long before the development of heart failure as a rule. On examination of a series of electrocardiograms, the combination of these disorders with a dynamic change in the shape and direction of the *T* wave is always detected. In endocarditis lenta disorders of myocardial excitation and conduction develop not at the beginning, but at the peak of the disease, usually at the same time as heart failure or after it.

The causes of fever in heart failure often remain unclarified. What seems to be fever without any cause occurs both in patients with endocarditis lenta and in those with rheumatic heart diseases and atherosclerotic cardiosclerosis. The difference consists in the fact that fever in rheumatic heart disease and cardiosclerosis is caused by pneumonia occurring as a complication of severe heart failure, whereas fever in endocarditis lenta is caused by sepsis.

Focal pneumonia or pulmonary thromboembolism with perifocal pneumonia and not bacterial endocarditis is always the underlying factor of fever of unrecognized origin developing in patients with a long history of heart failure. This rule remains true even in cases when focal pneumonia develops into an abscess and when it is complicated by pleurisy with effusion. The diagnosis of bacterial endocarditis may be ruled out with assurance if signs of right-ventricular failure had been present in the patient for about six months before the beginning of fever.

In identifying the cause of fever in cardiac disease with recent heart failure, one should always bear in mind its possible association with bacterial endocarditis. That is why in all such cases it is necessary to search for petechiae repeatedly on the mucous membranes, determine the size of the spleen, test the urine to reveal signs of nephritis and repeat blood cultures for isolating the causative agent. The same principle should guide the differential diagnosis between bacterial endocarditis complicated by diffuse glomerulonephritis and the commonly encountered chronic glomerulonephritis with renal insufficiency.

The causative agent of bacterial endocarditis is localized in the blood stream, usually in the left heart. From this place bacterial emboli enter the arteries of the systemic circulation and may cause infarction in any organ. The clinical syndromes of meningitis, hemiplegia and subarachnoid haemorrhage which develop in young patients with a congenital or acquired heart disease and fever often prove to be a complication of bacterial endocarditis. Its diagnosis may be ruled out with confidence only in patients with mitral stenosis complicated by cardiac fibrillation. Pneumococcal pneumonia with signs of meningitis is combined with endocarditis of the aortic valve in about one third of cases (Hurst, 1974).

Many infectious diseases are marked by long-term fever. Their clinical picture is so specific in most cases that no great difficulties are experienced in recognizing them at the peak of the disease. In atypical cases, such as the pneumonic form of enteric fever or meningococcal bacteraemia without meningitis, for instance, the diagnosis is often delayed and sometimes the disease remains unrecognized. Patients with tuberculosis, brucellosis, typhoid fever and infectious mononucleosis are sometimes hospitalized in departments for internal diseases for the purpose of identifying the cause of fever. In former times this also applied to malaria, typhus and relapsing fever which are no longer to be found in the Soviet Union.

Tuberculosis

Tuberculosis is still the most common cause of fever of unrecognized aetiology in the group of infectious diseases. For a great length of time fever may be the only manifestation of tuberculosis of the liver, pericardium, female genitals, peritoneum and the mesenteric and mediastinal lymph nodes. Fever sometimes appears long before the other signs of miliary tuberculosis. X-ray studies are the final stage in the diagnosis of tuberculosis, but in some cases they are also incapable of solving all the complexities of differential diagnosis, particularly difficulties associated with the localization of the process in the peritoneum, retroperitoneal lymph

nodes and adnexa uteri. The overcoming of these difficulties is madi easier by studying symptoms and signs found in the patient before the fever, using trial therapy, bronchoscopy, biopsy, examinatior of the irrigation waters from the stomach and bronchial mucosa and other special methods of examination.

Examination of the fundus oculi in fever of unknown aetiology sometimes discloses miliary eruptions which in the early stages are pale yellow and round with boundaries that are not clearly defined.

X-ray studies at this time sometimes reveal no signs of tuberculosis. In appraising this sign it is essential to bear in mind that identical changes in the fundus are also found in sarcoidosis. Disseminated forms of tuberculosis often lead to affection of the liver. Laparoscopy or biopsy of the liver may be of great assistance in timely identification of the cause of long-term fever.

Protracted fever often precedes typical signs of the primary tuberculosis complex both in its abdominal and its pulmonary localization. The pulmonary component of this complex is of small dimensions and low density at the early stages of the disease and therefore cannot be detected on ordinary radiographs for some time. Tomography and magnified radiographs of the lungs demonstrate the pulmonary component of the complex, but the changes in the lymph nodes in the pulmonary root are usually detected not at the very beginning of the disease, but only in later stages of the infiltrate (Kshanovsky, 1974). Repeated examination of the patient may prove to be invaluable in identifying the cause of protracted fever and in planning further diagnostic work.

It is more difficult to disclose tuberculous lesions of the mesenteric nodes and serous membranes: it is precisely these lesions which are attended by long-term fever more frequently than other diseases. Rubinshtein (1949) points out that effusion into the serous cavities is very often so negligible that it is detected neither by physical methods of examination nor even by X-ray. Because of the difficulties in detecting the objective signs the diagnosis in such cases has to be made only from the results of a more or less lengthy follow-up of the course of the disease and the results of trial therapy which is often prescribed with due regard for indirect signs of the development of tuberculosis, such as Pirquet's and Mantoux tests.

General diminution in tuberculin sensitivity has lately been noted in persons infected and sick with tuberculosis. At the same time intensification of tuberculin allergy is found in some immunized patients. Attempts are made to overcome the difficulties encountered in the diagnostic evaluation of the results of these tests by means of additional blood tests and biochemical examinations performed prior to and after the administration of tuberculin. There is as yet no unanimity in appraising the diagnostic value of these

tests. That is why clinicians are sometimes obliged to resort to trial therapy in order to make the diagnosis.

Typhoid Fever

Typhoid fever begins with high temperature the cause of which is not at first clear. It is to be suspected in all cases when progressive fever begins in a healthy person, gradually grows within the first week and is attended by sharp headache and weakness. Relative bradycardia is a characteristic sign. The rise in fever is not attended by an adequate increase in the rate of cardiac contractions. Fever of a continuous type sets in on the second week of the disease, headache sharply diminishes and may even disappear completely in the third week. Fever gradually begins reducing in the third week and may completely disappear in the fourth week.

A recurrence develops after a small afebrile period of about one week. A 'stepwise' rise in temperature begins anew, but the total duration of the febrile period is much shorter than that of the first period. A third and even a fourth recurrence is encountered in rare cases. The recurrence sometimes develops immediately after the fever ceases. Diarrhoea with a 'pea soup' stool occurs in some cases during the febrile period, or constipation is sometimes encountered.

The causative agent may be isolated from the blood in the first ten days of the disease. In later periods blood cultures yield negative results. The causative agent of the disease may always be cultured from the blood at the beginning of a recurrence. The spleen is enlarged in the first week of the disease and stays enlarged till the end of the febrile period. During a recurrence it is enlarged anew. Dry rales are auscultated in the lungs at the beginning of the disease and that is why high temperature at the onset of typhoid fever is sometimes attributed to bronchitis. The pneumonic form of typhoid fever develops in rare cases. A typical roseolous eruption appears in the first week of the disease, usually on the skin of the abdomen and less frequently on the chest and back. In rare cases the rose spots are found on the thighs.

Vidal's test becomes positive no earlier than the second week of the disease, usually after the tenth day. In some cases, however, it is negative even in the third week of the disease and rarely stays negative for four weeks. It proceeds from this that the diagnosis of typhoid fever in the acute period of the disease cannot be ruled out on the basis of only one negative result of Vidal's test.

In uncomplicated cases of typhoid fever, the blood leucocyte count is reduced or normal and there is a relative increase in the lymphocyte count. The absolute number of neutrophils is usually reduced. Despite the considerable amplitudes of the fever there are

no chills as a rule, which makes it easier to distinguish typhoid fever from sepsis, abscesses, and malaria.

In immunized patients typhoid fever is far milder. The febrile period is shorter. Some patients do not complain of headache and do not take to bed throughout the entire period of illness. Vidal's test in these patients may be positive when they contract typhoid fever or other febrile diseases.

Brucellosis

Brucellosis (undulant fever) may be the underlying factor of protracted fever. It may begin acutely or gradually. Arthralgia, lumbar pain, subfebrile temperature and headache develop in the prodromal period. Fever increases gradually and often becomes wavelike. Elevation of body temperature is attended by chills followed by profuse sweating. Despite the high fever, the general condition of most patients is satisfactory. They retain consciousness and are active and even somewhat euphoric.

Combination of fever with arthralgia and lymphadenitis is a characteristic sign. The cervical lymph nodes are enlarged earlier and more frequently than the other nodes. The axillary and inguinal nodes are involved much less frequently. Enlargement of the mediastinal and mesenteric lymph nodes is found in some cases. In distinction from lymphogranulomatosis, in brucellosis the lymph nodes show no tendency for rapid enlargement. Arthralgia or arthritis develops in the acute period of brucellosis in more than half the cases. The large joints (shoulders, elbows, hips, knees, ankles) are usually involved. Fibrositis and cellulitis are encountered in 10-15 per cent of cases and are usually localized in the lumbosacral region. Moderate hepatomegaly and splenomegaly are found in the acute period of the disease in approximately 80 per cent of cases. Jaundice develops only in rare cases.

Bacteraemia in the acute period of the disease may be confirmed by blood, bone-marrow or urine cultures. In view of the hazard of infection, this method has not been accepted at all laboratories. Wright's and Huddleson's tests are among the widely used laboratory methods in the diagnosis of brucellosis. Their results are already positive on the fifth day of the disease. Growth in their titres during the disease belongs to the group of significant signs confirming the diagnosis of brucellosis. A negative result of these tests does not rule out the disease. Burnet's skin test is of no great diagnostic value because it may be positive even in healthy individuals.

In the acute febrile period brucellosis sometimes has to be differentiated from typhoid fever. These diseases differ in their epide-

miological history and the results of immunological tests. Particular attention during physical examination should be focused on the detection of a characteristic eruption of rose spots and relative bradycardia which occurs only in typhoid fever but never in brucellosis. Lymphadenopathy, myalgia, arthralgia and arthritis are often found in brucellosis, but are not characteristic of typhoid fever. The general condition of a patient with brucellosis is often satisfactory even when body temperature is high. Typhoid fever often causes a certain degree of inhibition and stupefaction even in vaccinated patients.

Meningococcal Sepsis

In most cases meningococcal sepsis is marked by severe general toxicosis, high fever, recurrent chills and sharp pain in the joints and muscles. Severe headache, occipital rigidity and, in rare cases, convulsions occur when meningitis develops. A copious eruption appears on the skin in approximately 70 per cent of cases. It is maculous in milder cases and petechial in severe cases. In fulminant forms of sepsis the patient loses consciousness within a few hours after the onset of the disease. The Waterhouse-Friderichsen syndrome sometimes develops in less acute cases. A copious petechial skin eruption appears simultaneously with the development of a severe collapse. The systolic arterial pressure falls below 80 mm Hg, the skin becomes covered with a sticky sweat and the pulse is frequent and sometimes irregular. Consciousness remains clear.

Haemorrhage into the adrenals underlies collapse in the Waterhouse-Friderichsen syndrome. This is precisely the explanation for the possibility of its development in other types of severe sepsis, in anticoagulant therapy, and in any other acute circulatory disorders in the adrenals. Pneumococcal meningitis, endocarditis or septicaemia may develop as a complication of pneumococcal pneumonia and pneumococcal diseases of the ear and the nasal sinuses.

Fever in malaria is marked by characteristic alternation of periods of chill, fever and sweating. The total duration of a single attack does not exceed seven to eight hours. Depending on the type of the causative agent, the attacks may occur daily or at intervals of one or two days. A tentative diagnosis is based on the clinical picture of the disease in combination with signs of haemolytic anaemia and splenomegaly. The diagnosis is confirmed by identifying one of the species of the malarial plasmodium in the blood. Malaria like typhus and leishmaniasis have been eliminated in the USSR; several new generations of Soviet physicians have never encountered these diseases: for them, consequently, the diagnosis of sporadic cases or cases brought in from other countries presents a problem.

Focal Infection

Fever may precede specific or local signs in the early stages of suppuration. Every physician has had to examine many patients in his practice with remittent fever and high leucocytosis in whom the clinical findings give grounds to presume the formation of an abscess the insistent search for which over a great length of time is unsuccessful. A classical example is paranephritis in which the formation even of a large abscess sometimes occurs without pain or other signs of local inflammation.

In the past there was a tendency to attribute protracted fever of unknown origin to a focal infection in the tonsils, dental roots or gall bladder. With no desire to question the skill of physicians in the past it should nonetheless be borne in mind that **apical abscesses** may be asymptomatic for many months and even years. In some cases their diagnosis is made only after X-ray of the teeth. The body temperature in these patients is often normal, sometimes subfebrile and high fever is encountered only in rare cases. When found, such abscesses must be removed. If fever continues after their removal, other foci of infection must be searched for. Such foci are most frequently found in organs localized below the diaphragm. It is particularly difficult to diagnose inflammatory processes localized under the diaphragm or under the liver.

Subdiaphragmatic abscess is a rare disease. It may occur acutely, or develop insidiously. In most cases the abscess is a complication of other diseases. Most commonly it develops after operation for gastric and duodenal ulcer, after cholecystitis, acute appendicitis and pancreatitis. In about 10 per cent of cases its causes remain unknown.

The clinical picture of the disease is determined by the localization of the abscess. It may form under the apex of the diaphragmatic cupola, or under its right or left, anterior or posterior part. Approximately three fifths of all the abscesses are found under the right diaphragmatic cupola. More than one third are localized on the left above the spleen. Bilateral abscesses are encountered in rare cases.

It is very difficult to make the diagnosis of subdiaphragmatic abscess, particularly when the purulent effusion occurs between the liver and the diaphragm as a thin layer and when X-ray fails to demonstrate the characteristic fluid level with gas accumulated above it.

In most cases the disease begins with fever, vomiting and pain in the hypochondrium. Tapping of the hypochondrium produces sharp pain. The pain is usually referred to the back or lumbar region and much less frequently to the arm and supraclavicular region.

Body temperature increases in the evening and is attended by chills. High leucocytosis and increased ESR are found in the blood. Physical examination reveals diminished breathing and a dulled percussion sound on the affected side at the very onset of the disease. This is caused by the high position of the diaphragm in some cases and by accumulation of effusion in the pleural cavity in others. X-ray examination easily distinguished these syndromes from one another. The localization of the abscess is determined by the level of the fluid and the gas above it. The diagnosis of subdiaphragmatic abscess is verified by removing pus from its cavity during exploratory puncture.

According to Karavanov and Danilov (1975), the diagnosis of subdiaphragmatic abscess is made with considerable delay as a rule. An average of 34 days passes from the time of the operation after which the subphrenic abscess had developed to the time the diagnosis is made.

It is even more difficult to establish the diagnosis of **subhepatic abscess** developing as a complication of purulent cholecystitis or atypical perforation of gastric ulcer. The clinical picture of subhepatic abscess consists of fever, pain in the epigastrium and right hypochondrium, severe toxicosis and subicteric skin. Leucocytosis with a shift to the left and increased ESR are found in the blood. Laporoscopic examination proves valuable in cholecystogenic origin of the subhepatic abscess; the state of the gall bladder may be appraised and fresh adhesions may be found in the upper abdomen during this examination.

Cholangitis and abscess of the liver. The clinical picture of cholangitis is marked by pain, jaundice and fever. These three syndromes usually occur simultaneously, but in rare cases fever is the only manifestation of the disease for a lengthy period of time.

Chronic cholangitis without suppuration and without obstruction of the biliary ducts is usually marked by long-term subfebrile temperature and periodical exacerbations of the disease. They are manifested by more or less long periods of fever with chills, abdominal pain and jaundice. The chills and fever result from entry of the causative agents of cholangitis into the blood; most commonly this is *Escherichia coli*, the 'main parasite' of the biliary tract. The pure culture of the causative agent is often isolated if blood for the culture is taken before the beginning of the chill. In this type of cholangitis fever usually ceases spontaneously or under the effect of antibiotics and is not attended by toxicosis.

The disease develops slowly and the patient's general condition may be satisfactory for many years. Exacerbation of the disease usually develops in impaired flow of the bile. Jaundice appears usually in 24 hours when the gall bladder does not function or in two to four days after total obstruction of the common bile duct

when the function of the gall bladder is maintained. Purulent cholangitis may occur if bile drainage is not restored.

Acute purulent cholangitis is caused by the same factors as chronic cholangitis, namely, obstruction of the common bile duct by a stone and its stenosis by cicatricial tissue or a tumour. The possibility of acute purulent cholangitis must be considered in every patient with high fever attended by chills, pain in the right hypochondrium, leucocytosis and severe symptoms of toxicosis. The diagnosis of acute purulent cholangitis is highly probable when antibiotic therapy applied for five to six days fails to bring about improvement in the patient's general condition or relieve the chills and fever. Physical examination always reveals an enlarged and tender liver and jaundice of this or that degree.

The patient's severe general condition and shaking chills recurring throughout the day are explained by sepsis. Blood cultures are necessary not only for detecting bacteraemia, but for testing the sensitivity of the causative agent to antibiotics. The disease is often complicated by abscesses of the liver, which are sometimes small and multiple and at other times solitary and extensive. Acute purulent cholangitis and liver abscesses are mostly encountered in departments for internal diseases as complications in the late stages of carcinoma of the head of the pancreas or other diseases marked by compression of the common bile duct. In some cases abscess of the liver is a complication of pyelophlebitis occurring after an abdominal operation performed long before. Abscesses of the liver caused by intestinal amoeba are encountered in the southern regions of the Soviet Union. In the northern regions this complication is encountered extremely rarely. In our many years of experience we came across this complication only once.

Abscesses of the liver (multiple or solitary) are localized in the right lobe as a rule. Their clinical picture depends to a great measure on the localization. Intrahepatic abscesses cause no pain, but the patient experiences a feeling of heaviness in the right hypochondrium. Sharp pain in the right half of the chest is felt in subscapular localization of the abscess. Hectic fever with chills recurring throughout the day and severe toxicosis appear before the formation of the abscess. High leucocytosis with a shift to the left and increased ESR are found in the blood. The liver is enlarged both in its upper and lower parts. Palpation of its lower margin elicits tenderness in most cases. Its upper boundary is raised to the level of the fifth rib. The right diaphragmatic cupola does not take part in the respiratory excursions. An effusion is often found in the right pleural cavity in which case the dull percussion sound over the right lung spreads upward to the level of the fourth and even the third rib. The fluid in the pleural cavity may be serous or purulent. The abscess may open into any of the adjacent organs: into the pleural

cavity, stomach, the abdominal cavity and the retroperitoneal space. In most cases, however, the patient dies from toxicosis before these complications develop.

Chronic pyelonephritis may be marked by normal temperature or by fever. In a patient with lumbar pain, dysuria, pyuria and bacteriuria the cause of fever is quite obvious. Unfortunately for physicians these signs are so inconspicuous in some cases of pyelonephritis marked by protracted fever that they are revealed only after long and persistent search. Such difficulties are encountered particularly often in children and the aged.

Paranephritis and paranephral abscess are marked by protracted fever with chills, leucocytosis and increased ESR. Pasternatskii's sign is usually positive. By the time the abscess forms patients almost always complain of spontaneous pain in the small of the back or in the lateral part of the abdomen. In the first weeks these pains may be absent, in which case fever is the main, if not the only syndrome of the disease. Examination of the paranephral region does not always reveal the tumour, but increased rigidity of the muscles on the affected side is detected in almost all cases.

Paranephritis and paranephral abscess are, in most cases, a consequence of the spread of purulent inflammation from the kidneys. We had a few cases with paranephritis which had developed after retroperitoneal (retrocaecal) appendicitis. Cases of paranephritis have been described which had developed following a carbuncle of the lumbar region or after affection of a haematoma caused by a trauma. In taking the medical history one should always bear in mind that an abscess may develop in the paranephral region several months after injury.

Bronchiectases with suppuration. Fever, the cause of which sometimes remains unclear for a long time, may be a consequence of suppuration of bronchiectases or inflammation of their wall. Elevation of body temperature is often attended by a shaking chill, while its fall is accompanied by profuse sweating. In patients with bronchiectases the periods of fever usually alternate with afebrile periods.

The true cause of fever is identified with difficulty only when the disease develops without the discharge of sputum. In such cases the inflammatory process is localized in the bronchial wall or in the pulmonary parenchyma around the bronchus. The foci of this 'perifocal pneumonia' may be small and therefore they are not always demonstrated on ordinary roentgenograms. After a course of antibiotic therapy fever usually disappears for quite a lengthy period of time and then recurs because of overcooling. Fever may possibly occur in association with reinfection of bronchiectases or with reactivation of already existing flora under the effect of unfavourable environmental conditions.

Diffuse Diseases of the Connective Tissue

Fever is encountered practically in every case of acute rheumatism, Crohn's disease, systemic lupus erythematosus, nodular periarteritis and rheumatoid arthritis. The diseases mentioned may be conditionally referred to the group of collagenosis. Secondary infection developing in attendance to the principal disease may also be the cause of protracted fever. It should also be remembered that drug fever is a particularly frequent occurrence in this group of diseases. The association of fever with diseases included in the group of collagenosis may be presumed only after its connection with the drugs that were applied is ruled out.

Fever often predominates in the clinical picture of **systemic lupus erythematosus.** Elevations of body temperature may be attended by chills and profuse sweating, but general toxicosis is usually mild. The patients prove to be capable of speaking coherently about their disease even when their temperature is very high. Fever in systemic lupus erythematosus is absolutely resistant to antibiotics and sulphanilamides but is very sensitive to antipyretics and steroid hormones. It is accompanied by leucopenia, as a rule. The blood eosinophil count is often normal.

Fever in systemic lupus erythematosus is rarely isolated. In most cases arthralgia and erythema or purpura develop simultaneously with it. High body temperature is always encountered in rapid generalization of the process with involvement of the joints, lymph nodes, pleura, pericardium and kidneys. An acute course of systemic lupus erythematosus is encountered usually in young persons and particularly often in females.

The diagnosis may be considered established if, during the apparently asymptomatic fever, characteristic changes are detected on the skin of the nose and cheeks in the shape of a 'butterfly' and if repeated blood tests show L. E. cells or the antinuclear factor in a high titre. The typical multisystemic character of the affection usually becomes evident only in the later stages of the disease. Involvement of the kidneys and lymph nodes is of particular diagnostic significance. Biopsy of these organs may greatly help to identify the cause of the protracted fever.

Fever at the onset of systemic lupus erythematosus in many respects resembles fever in **rheumatoid arthritis** from which it often has to be distinguished. About half of the cases of rheumatoid arthritis begin with polyarthritis and about one third of cases, with monoarthritis.

In adolescence rheumatoid arthritis in one tenth to one fifth of cases sets in with fever which may not be attended by arthritis

for quite a lengthy period of time. Fever at the onset of rheumatoid arthritis (like in systemic lupus erythematosus) is often attended by arthralgia and skin eruptions occurring only during the febrile period. The rise in body temperature may be accompanied by chills. For one or three weeks body temperature stays at a level of 38-40°C after which an afebrile period develops.

At a later period the disease gradually acquires a typical multisyndrome character with involvement of the pleura and lungs and with enlargement of the spleen and lymph nodes simultaneously with the fever. Polyarthralgia is replaced by arthritis. The polycyclic course of juvenile rheumatoid arthritis must be differentiated from other forms of collagenosis and tumours. The differential diagnosis with lupus arthritis is particularly difficult. In distinction from systemic lupus erythematosus, rheumatoid arthritis is characterized by stiffness experienced by the patient in the morning.

These two diseases may be differentiated from each other by the character of the skin lesions. Systemic lupus erythematosus is marked by skin vasculitides, which are not characteristic of rheumatoid arthritis. Changes on the skin of the face with the formation of the characteristic 'butterfly' are only encountered in systemic lupus erythematosus. The findings of kidney biopsy help greatly in the differential diagnosis. The typical histological picture of lupus nephritis marked by the presence of 'wire loops', fibrinoid, hyalin thrombi and abnormalities in the nucleus is found only in systemic lupus erythematosus. Leucopenia is often found in the blood during the febrile period in systemic lupus erythematosus, whereas rheumatoid arthritis is characterized by neutrophilic leucocytosis. Unfortunately, the differential diagnostic signs mentioned above cannot always be detected in every case of fever.

The clinical picture in rheumatoid arthritis may resemble sepsis, the beginning of the arthritic form of psoriasis and brucellosis. The results of the test for the rheumatoid factor (which in most of these patients is detected in the early stages of the disease) help to identify the true cause of the fever. Reduced complement level is often found in the blood and the synovial fluid. Biopsy of the synovial tissue of the joint may assist in the establishment of the diagnosis.

Protracted fever often occurs in **periarteritis nodosa**, both in the idiopathic and the drug forms. The disease usually sets in suddenly with high fever and severe toxicosis. The urinary syndrome, loss of body weight, attacks of paroxysmal dyspnoea and moderate or marked increase of arterial pressure soon join the fever. In drug vasculitides developing after medication with penicillin, ceporin and diuretics, abdominal pain appears simultaneously with the fever. The multisystemic affection is detected much earlier in acute periarteritis nodosa, than in other forms of collagenosis; this must

be borne in mind in making the differential diagnosis. High importance is attached to affection of the kidneys. Arterial hypertension appears in these patients usually at the same time as the urinary syndrome. The results of biopsy of the kidneys, subcutaneous nodules or muscles may be a valuable aid in making the diagnosis.

Crohn's disease is marked by fever in 33-41 per cent of cases. In uncomplicated cases body temperature is elevated to 38° C and higher, usually with no chill. The drop in temperature is rarely attended by sweating. It is even claimed that sweating is an indication of tuberculosis of the small intestine rather than of Crohn's disease. About a year sometimes elapses from the beginning of fever till the diagnosis is established. During this time the fever is not attended by any noticeable disorders in the function of other organs. Abdominal pain is encountered much more frequently than fever, but Crohn's disease is usually suspected only after diarrhoea appears.

In considering the cause of the abdominal pain and fever, it is necessary to take the patient's age into account. At elderly and old age fever with pain in the abdomen is usually more frequently caused by diverticulitis or carcinoma of the large intestine than by Crohn's disease. Diarrhoea concomitant with fever is a constant sign in Crohn's disease, whereas in diverticulitis and carcinoma of the colon diarrhoea alternates with constipation.

Tumours

Fever always occurs in this or that developmental stage of a tumour. In many cases it is induced by concomitant infection. Fever in bronchogenic carcinoma may serve as an example, it often is a consequence of pneumonia of a deficiently ventilated area of the lungs. Fever may also occur under the effect of the tumour itself. Two hypotheses of the origin of fever in tumours have been suggested. Some authors believe that the growing tumour secretes pyrogenic agents which cause an effect on the thermoregulation centres and induce fever. According to other authors, fever occurs under the effect of necrosis of the rapidly growing tumour.

After leucocytic infiltration of the necrotic tumour areas, an inflammatory reaction develops in them. This reaction is similar to the inflammatory reaction developing in the myocardium suffering an infarction.

Fever in tumours may be continuous, asthenic or intermittent. From time to time it is attended by chills. Fever is encountered in any type of tumour, but is a particularly constant occurrence in malignant tumours of the kidneys, liver and lymphoid tissue.

Tumours of the kidneys. Approximately 11-12 per cent of patients with hypernephroid carcinoma apply to the doctor for the first

time because of protracted fever for which there seems to be no reason. It has been pointed out that fever is sometimes the only symptom of the disease. Fever in such cases is attended by marked anorexia as a consequence of which the patient rapidly loses weight and general weakness increases.

The combination of haematuria with pains and a palpable tumour is considered a classical triad of hypernephroma. Fever in such cases appears before the palpable tumour and from the practical point of view the combination of haematuria with lumbar pain and fever should therefore be regarded as the main diagnostic triad. In many cases of hypernephroma hepatomegaly, splenomegaly and increased concentration of alkaline phosphatase in the blood appear simultaneously with the fever. According to some authors, enlargement of the liver and disturbance of its secretory function in hypernephroma cannot be explained by metastatic spread of the tumour because they often disappear soon after removal of the tumour.

Despite the moderate or even high fever, arterial pressure in hypernephroma is often increased. The combination of fever with arterial hypertension may be included among the early manifestations of hypernephroma and should be considered as grounds for detailed urological examination of the patient.

Particular attention should be attached to questioning the patient about the pain sensations in the abdomen and lumbar regions. These pains are often very moderate and the patient mentions them only if the physician makes a point of finding this out. Hypernephroma is suspected only after the appearance of macrohaematuria which often occurs suddenly in a patient whose general condition is quite satisfactory. Haematuria disappears in a few days. Microhaematuria occurs somewhat less frequently.

Hypernephroma is among the tumours which metastasize early. Its timely diagnosis may only be made when complete urological examination of the patient has been undertaken in the stage preceding haematuria and the palpable tumour. In about 12 per cent of cases fever proves to be one of the earliest signs of hypernephroma, and when all its other possible causes have been ruled out not only excretory urography, but renal arteriography or renal venography should be conducted.

The need to recommend selective arteriography is linked with the fact that only small tumours are manifested by fever and they may be detected only by this method.

Tumours of the liver are often marked by protracted fever which is caused either by an attendant infection or by growth of the tumour itself. It is easy to guess the cause of fever in a patient with hepatomegaly, cachexia, jaundice and ascites, and far more difficult to identify its cause when it is the only sign of malignant tumour of the liver. It was reported that metastasis of a malignant tumour

to the liver in 7 per cent of cases was manifested only by fever.

In the last 10-15 years new methods for the examination of the liver have been used, which make it possible to detect even very small tumours without harm to the patient's health. Isotope scanning demonstrates tumours and other hepatic masses of more than 2 cm in diameter. Selective arteriography reveals tumours of the liver 1 cm in diameter. Needle biopsy of the liver is among the less precise diagnostic methods, which have nonetheless proved their worth. The tumour may be located by isotope scanning or liver arteriography. Subsequent transcutaneous biopsy in the place indicated sometimes determines the character of the tumour and, consequently, identifies the cause of protracted fever.

Persistent fever is sometimes caused by a small tumour of the biliary tract, for the detection of which it is recommended to undertake cholecystography and ascending cholangiography performed during panendoscopy. Laparoscopy may also greatly help in detecting a tumour in the abdominal cavity, particularly if it is combined with spot biospy, cholecystography and cholangiography.

Lymphogranulomatosis and lymphosarcoma. Lymphogranulomatosis is attended particularly often by fever, the cause of which may be unclear for a long time. During fever the lymph nodes involved in the process are rapidly enlarged. After the temperature becomes normal, they appear noticeably smaller. The mediastinal lymph nodes are affected most frequently. Their size varies sharply with each patient. Enlargement of the right paratracheal nodes is noted most frequently. Enlargement of lymph nodes at the root of the lungs and of nodes localized at the bifurcation of small bronchi is encountered much less frequently. Their slight enlargement may be detected only on tomograms.

The mesenteric, intestinal and retroperitoneal lymph nodes are often involved in haematosarcoma, but very rarely in lymphogranulomatosis. For many years the size of these nodes was judged from the results of palpation. Involvement of these nodes in the process is also judged by the presence of oedema in the lumbar region. Later their size began to be appraised from the results of cavagraphy and urography.

These methods demonstrate only considerably enlarged lymph nodes because only such large nodes may cause characteristic displacement of the ureters and vena cava inferior. The size and localization of the retroperitoneal lymph nodes are now easily determined by isotope lymphangiography.

Lymphogranulomatosis and haematosarcoma of the small intestine and colon are usually diagnosed in the late stages. Primary affection of the stomach and intestine is very rare. According to some authors, in such cases fever is combined with diarrhoea and cachexia, as a rule, and only very rarely may be related to fevers of unknown

aetiology. It is more difficult toi dentify the cause of fever in primary localization of the disease in the wall of the urinary bladder, the oesophagus, the wall of the stomach or the vermiform process.

Most patients with lymphogranulomatosis seek the advice of a doctor because of enlargement of lymph nodes on the neck, in the axillae or in the abdomen. Approximately one third of these patients have fever, the cause of which becomes obvious after biopsy of the enlarged nodes. Diagnostic difficulty arises when lymph nodes inaccessible to palpation are involved in the process, i.e. nodes localized in the abdominal cavity, retroperitoneally, in the true pelvis, in the lungs and in the mediastinum. In such cases fever is at first attributed to intercurrent diseases. Regular diagnostic examination is begun only when it becomes obvious that the initial diagnosis was incorrect.

Undulating fever is characteristic of far-advanced cases of lymphogranulomatosis. In the early stages this disease is marked by short-term, often nocturnal elevations of temperature, sometimes to 40-41° C, which are followed by profuse sweating. By morning the body temperature may be normal. Skin itching sometimes occurs at the same time as the fever. In 2-5 per cent of patients with lymphogranulomatosis alcohol induces pain in the enlarged lymph nodes. The pain begins a few minutes after taking alcohol, lasts from several minutes to an hour and may terminate in vomiting. Nausea and vomiting may occur instead of pain. Enlargement of the liver and spleen occurs in the later stage of the disease, which makes the diagnosis much easier.

In the early stages of lymphogranulomatosis, focal and not diffused affection of the bone marrow occurs so that sternal puncture at the onset of the disease rarely yields valuable diagnostic information. Diagnostic importance should be attached only to positive results of bone marrow examination. The absence of Sternberg-Berezovsky's cells in the aspirated material does not rule out lymphogranulomatosis. Many authors recommend performing diagnostic laparotomy when the indirect clinical findings allow affection of the abdominal or retroperitoneal lymph nodes to be suspected but the diagnosis cannot be established from the information gained by the methods mentioned above (and consequently the causes of the fever cannot be clarified).

Other Diseases

Fever may be the only manifestation of myelocytic leucosis, particularly its aleukaemic phase for a lengthy period of time. In lymphoid leucosis and myeloma fever is most likely to develop

under the effect of a concomitant infection. Other **diseases of the blood** are also very often attended by fever which is caused by secondary infection in aplastic anaemia and agranulocytosis. Severe anaemia of any origin is complicated by fever which may be as high as 38-39° C. Fever in severe pernicious anaemia just as fever in haemolytic anaemia is probably associated with red-cell disintegration.

Thrombophlebitis is often the cause of protracted fever attended by leucocytosis, increased ESR and sometimes also by chills. Superficial thrombophlebitis is easily recognized. The diagnosis of inflammation of the veins of the pelvic organs and the deep veins of the limbs is a far more difficult task. Fever in such cases may be sustained not only by the inflammatory process in the veins themselves, but also by microfocal inflammation of the lungs caused by their microembolization from the veins of the pelvis and lower limbs.

Protracted fever is often encountered in patients suffering from **chronic hepatitis and cirrhosis of the liver.** It is possibly caused by enterogenic bacteraemia or may be by the effect of pyrogenic agents liberated as a result of the continuously occurring necroses of the liver. The presumption that the fever is associated with a disease of the liver may be considered substantiated only when all other causes of its development are ruled out.

Rare cases of **diffuse** or **nodular goitre** are encountered in which all other signs of thyrotoxicosis with the exception of fever are hardly or not at all visible. Two or three months may elapse before any proof of the connection of fever with thyrotoxicosis is disclosed. The duration of this interim may be noticeably shortened if the existence of 'monosymptomatic' forms of thyrotoxicosis is acknowledged. This term is used to designate thyrotoxicosis in the clinical picture of which one of the syndromes alone is predominant, fever, for instance.

In our practice we encountered such cases of protracted fever caused by thyrotoxicosis about once or twice a year, and always either in elderly or old individuals. Tachycardia in such patients is usually regarded as a consequence of fever. This seems probable because of the insufficiently manifested ocular symptoms of thyrotoxicosis. The thyroid in these patients is normal in size or only slightly enlarged. The association of protracted fever with thyrotoxicosis becomes obvious only after a test for thyroxine concentration in the blood serum. The final diagnosis is based on the results of therapy. The method of diagnostic work in such a type of patients is discussed in greater detail in the chapter 'Goitre with Signs of Thyrotoxicosis'.

In some cases fever proves to be the only manifestation of drug intolerance. Fever develops particularly frequently in a patient

treated with sulphanilamides, antibiotics (penicillin, tetracycline, vancomycin, streptomycin, etc.), hypotensive agents (aldomet, hydrolysine, etc.), diuretics (novurit, acetazolamide, hydrochlorothiazide), antiarrhythmic agents (quinidine, novocainamide, etc.) and many other agents.

Drug fever begins between the 7th and 10th day of medication, on the average. Continuous or remittent fever grows gradually to 39-40° C and stays at this level until the agent which had caused it is discontinued. Leucocytosis with a shift to the left is sometimes as high as $20 \cdot 10^3$-$30 \cdot 10^3$ per 1μl. The eosinophil count increases in rare cases. Temperature returns to normal level two or three days after the drug which had caused it is discontinued. Repeated medication with the drug results in recurrence of the fever. During the increased body temperature chills are often encountered.

It is always difficult to diagnose drug fever and at first only a tentative diagnosis may be made. As it was stated above body temperature increases gradually and the patient's condition is quite satisfactory. Later, when it stays at 39-40° C, no toxicosis adequate to the severity of fever and, in some cases, no leucocytosis are found in the patient. Somewhat later other signs of hypersensitivity of the patients to the drug join the fever: measles-like rash, purpura, urticaria. Complications which are more severe (arteritis with focal necroses, dermatitis exfoliativa, haemolytic anaemia, thrombocytopenia and other haematological reactions) are encountered much less frequently.

Drug fever develops either as an allergic reaction or as a consequence of the direct toxic effect of the drug on some organ. The development of the syndrome of systemic lupus erythematosus under the effect of hydrolysine is the most vivid example of drug fever of the first type. Fever in necroses of the liver induced, for instance, by monoamine oxidase inhibitors, halothane and other hepatotoxic agents is an example of the second type of fever.

For a long period of time fever may be the principal or even the sole manifestation of the disease. To identify its cause it is sometimes necessary to study anew the patient's epidemiological history, occupation, the character of his harmful habits and the diseases suffered in the past. The results of repeated objective examination of the patient with the use of practically all modern methods, including surgery, are of no less importance. Overly long passive observation of the natural course of the disease cannot be recommended as standard tactics at the bedside of patients with fever of unknown origin. Timely exploratory laparotomy may disclose, for instance, an operable tumour, whereas observation over the course of the disease may lead to a diagnosis which is correct but late. The diagnostic significance of trial therapy should not be overestimated either. The prescription of short-term antibiotic ther-

apy instead of performing a blood culture, for instance in a case with suspected bacterial endocarditis, may result in the disappearance of fever which recurs after antibiotics are discontinued.

In some cases the cause of fever remains unclear even after the application of all accessible diagnostic methods. In our practice we encountered patients with fever which persisted for six months and disappeared spontaneously. Its cause remained unknown. Moreover, rare cases are encountered in which the cause of protracted fever cannot be identified even after detailed study of the clinical and pathological findings.

Supplement X-1

The Most Common Causes of Fever of Unknown Aetiology

I. Artificial fever.
II. Constitutional hyperthermia.
III. Infection
  A. General infection.
    1. Sepsis
      Septicaemia.
      Pyaemia.
      Bacterial endocarditis.
    2. Tuberculosis.
    3. Typhoid fever.
    4. Brucellosis
    5. Meningococcal sepsis.
    6. Malaria.
  B. Focal infection.
    1. Apical granuloma.
    2. Subphrenic abscess.
    3. Subhepatic abscess.
    4. Cholangitis and abscess of the liver.
    5. Pyelonephritis.
    6. Paranephritis.
    7. Bronchiectases with suppuration.
IV. Diffuse diseases of the connective tissue.
    1. Systemic lupus erythematosus.
    2. Rheumatoid arthritis.
    3. Periarteritis nodosa.
    4. Crohn's disease.
V. Tumours.
    1. Tumours of the kidneys.
    2. Tumours of the liver.
    3. Lymphogranulomatosis.
    4. Lymphosarcoma.
  Other diseases.
    1. Diseases of the blood and haematopoietic organs.
    2. Thrombophlebitis.
    3. Chronic hepatitis and cirrhosis.
    4. Thyrotoxicosis.
    5. Drug fever.

Supplement X-2

Diseases in Which Fever is Naturally Complicated by Chills

1. Sepsis.
2. Bacterial endocarditis.
3. Abscess formation in any organ.
4. Bacterial pneumonia.
5. Thrombophlebitis and pyelophlebitis (purulent).
6. Cholangitis (purulent).
7. Malaria.
8. Bronchiectasis.
9. Erysipelas.
10. Paranephritis and pyelonephritis.
11. Acute leucosis.
12. Empyema of the pleura.